EXPLORING THE LINK BETWEEN VITAMIN D DEFICIENCY AND PREDIABETES IN THE IBB GOVERNORATE, YEMEN: THE PREVALENCE AND IMPACT OF HIGH-DOSE VITAMIN D SUPPLEMENTATION

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27 August 2026 MOHAMMED ABDO MOHAMMED YASEEN AL-HETAR
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ABSTRAK

Pradiabetes dan kekurangan vitamin D merupakan isu kesihatan awam yang saling berkaitan, khususnya di kawasan berpendapatan rendah dengan kadar penyakit metabolik dan hipovitaminosis D yang tinggi. Kajian ini bertujuan menentukan prevalens pradiabetes dalam kalangan dewasa di Wilayah Ibb, Yemen; menilai prevalens kekurangan vitamin D dalam kalangan individu pradiabetik berdasarkan kriteria Persatuan Diabetes Amerika (ADA); serta menilai kesan suplemen vitamin D dos tinggi terhadap parameter glisemik, rintangan insulin, fungsi sel β, keradangan, dan fungsi endotelium.

Kajian dua fasa dijalankan antara Julai 2024 dan Mei 2025, melibatkan kajian keratan rentas berasaskan komuniti dan percubaan rawak, buta berganda serta terkawal plasebo. Seramai 1,045 orang dewasa berumur 18–60 tahun disaring. Pradiabetes ditakrifkan mengikut kriteria ADA menggunakan glukosa darah berpuasa (FBG), glukosa plasma 2 jam selepas makan (2HPP), atau HbA1c. Daripada 266 dewasa dengan pradiabetes, 151 mempunyai kekurangan vitamin D dan secara rawak menerima sama ada koleskalsiferol oral 50,000 IU setiap minggu atau plasebo selama 16 minggu. Status vitamin D dikategorikan sebagai kekurangan (<20 ng/mL), ketidakcukupan (20–30 ng/mL), atau mencukupi (>30 ng/mL).

Hasil utama kajian ialah prevalens pradiabetes, prevalens kekurangan vitamin D dalam kalangan pradiabetes, serta perubahan FBG, 2HPP, HbA1c, HOMA-IR dan HOMA-β. Hasil sekunder termasuk hs-CRP, IL-6, profil lipid, dan fungsi endotelium melalui dilatasi berasaskan aliran (FMD).

Prevalens pradiabetes berdasarkan FBG ialah 23.4% (n=245), 14.7% (n=154) berdasarkan 2HPP, dan 26.4% (n=276) berdasarkan HbA1c. Dalam kalangan 266 peserta pradiabetes, 74.1% (n=197) mengalami kekurangan vitamin D, 19.2% (n=51) ketidakcukupan, dan 6.7% (n=18) mencukupi. Selepas intervensi, paras 25(OH)D meningkat dengan signifikan dalam kumpulan vitamin D berbanding plasebo (31.13±6.42 vs 10.64±4.87 ng/mL; p<0.001). Suplemen vitamin D menunjukkan kesan signifikan dalam menurunkan FBG (94±8.1 vs 100±9.3 mg/dL; p<0.001), meningkatkan fungsi sel β (HOMA-β: 94.79±22.6 vs 72.16±19.4; p=0.028), dan memperbaiki FMD (15.47±3.2% vs 2.72±1.1%; p<0.001). Tiada perbezaan signifikan dicatatkan bagi HbA1c, 2HPP, HOMA-IR, IL-6, hs-CRP, atau profil lipid.

Kesimpulannya, prevalens pradiabetes dan kekurangan vitamin D adalah tinggi dalam kalangan dewasa di Ibb, Yaman. Suplemen vitamin D dos tinggi dapat memperbaiki glukosa puasa, fungsi sel β, dan fungsi endotelium, sekali gus menyokong peranannya sebagai strategi tambahan dalam pengurusan awal risiko metabolik dan vaskular

ABSTRACT

Prediabetes and vitamin D deficiency are interrelated public health concerns, especially in low-resource regions with high metabolic risk. This study aimed to determine the prevalence of prediabetes among adults in Ibb governorate, Yemen, assess vitamin D status in ADA-defined prediabetic individuals, and evaluate the effects of high-dose vitamin D supplementation on glycaemic parameters, insulin resistance, β-cell function, inflammatory markers, lipid profile, and endothelial function. This two-phase study, conducted from July 2024 to May 2025, included a community-based cross-sectional study followed by a randomized controlled trial involving 1,045 adults aged 18–60 years. Prediabetes was defined using American Diabetes Association criteria based on fasting blood glucose (FBG), 2-hour postprandial plasma glucose (2HPP), or glycated hemoglobin (HbA1c). Of 266 adults with ADA-defined prediabetes, 151 who had vitamin D deficiency were randomised to receive weekly oral cholecalciferol 50,000 IU or placebo for 16 weeks. Vitamin D status was categorized as deficient (<20 ng/mL), insufficient (20–30 ng/mL), or sufficient (>30 ng/mL). Primary outcomes were prediabetes prevalence, vitamin D deficiency among prediabetics, and changes in glycaemic parameters and insulin indices (FBG, 2HPP, HbA1c, HOMA-IR, and HOMA-β). Secondary outcomes included hs-CRP, IL-6, lipid profile, and endothelial function measured by flow-mediated dilation (FMD). Prediabetes prevalence was 23.4% (n=245) (FBG), 14.7% (n=154) (2HPP), and 26.4% (n=276) (HbA1c). Among 266 prediabetics, 74.1% (n=197) were vitamin D deficient, 19.2% (n=51) insufficient, and 6.7% (n=18) sufficient. Post-intervention, 25(OH)D level increased significantly in the vitamin D group compared with placebo (31.13 ± 6.42 vs. 10.64 ± 4.87 ng/mL; p<0.001). Vitamin D supplementation significantly reduced FBG (94 ± 8.1 vs. 100 ± 9.3 mg/dL; p<0.001), improved β-cell function (HOMA-β: 94.79 ± 22.6 vs. 72.16 ± 19.4; p=0.028) and endothelial function (FMD: 15.47 ± 3.2% vs. 2.72 ± 1.1%; p<0.001) compared with placebo. No significant differences were observed for HbA1c, 2HPP, HOMA-IR, IL-6, hs-CRP, or lipid parameters between groups. In conclusion, prediabetes and vitamin D deficiency are highly prevalent in Ibb governorate. High-dose vitamin D supplementation improves fasting glycemia, β-cell function, and endothelial function, supporting its potential role as an adjunct strategy for early metabolic and vascular risk modification in vitamin D-deficient prediabetics.

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LIST OF ABBREVIATIONS

Abbreviation	Full Form
$1,25(OH)_2D_3$	1,25-Dihydroxyvitamin D_3
25(OH)D	25-Hydroxyvitamin D
2HPP	2-hour Postprandial Blood Glucose
AI	Adequate Intake / Artificial Intelligence (context-dependent)
ANOVA	Analysis of Variance
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CRP	C-Reactive Protein
DRI	Dietary Reference Intake
EAR	Estimated Average Requirement
ECLIA	Electrochemiluminescence Immunoassay
ELISA	Enzyme-Linked Immunosorbent Assay
eNOS	Endothelial Nitric Oxide Synthase
FBS	Fasting Blood Sugar
FMD	Flow-Mediated Dilation
FN	First Nations
FPG	Fasting Plasma Glucose
FBS	Fasting Blood Sugar
FPI	Fasting Plasma Insulin
FSL	Fasting Serum Lipid
GENNID	Genetics of Non-Insulin Dependent Diabetes
HDL-C	High-Density Lipoprotein Cholesterol
HOMA-B	Homeostasis Model Assessment of β-cell Function
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
HPLC	High-Performance Liquid Chromatography
hs-CRP / HSCRP	High-Sensitivity C-Reactive Protein
IFG	Impaired Fasting Glucose
IGI	Insulinogenic Index

IGT	Impaired Glucose Tolerance
IL-6	Interleukin-6
IMP	Investigational Medical Products
IOM	Institute of Medicine
IR	Insulin Resistance
ISOGTT	Insulin Sensitivity Index from Oral Glucose Tolerance Test
IssI-2	Insulin Secretion Sensitivity Index 2
IU	International Unit
LDL-C	Low-Density Lipoprotein Cholesterol
LFT	Liver Function Test
MAR	Missing at Random
MCAR	Missing Completely at Random
Mets	Metabolic Syndrome
MENA	Middle East and North Africa.
NF-κB	Nuclear Factor Kappa B
Non-HDL	Non-High-Density Lipoprotein Cholesterol
OGTT	Oral Glucose Tolerance Test
PTH	Parathyroid Hormone
RCT	Randomized Controlled Trial
RDA	Recommended Dietary Allowance
RP	Renal Profile
SD	Standard Deviation
SE	Standard Error
SPSS	Statistical Package for the Social Sciences
T2DM	Type 2 Diabetes Mellitus
TC	Total Cholesterol
TG	Triglycerides
Treg	T-regulatory cells
UL	Tolerable Upper Intake Level
UVB	Ultraviolet B Radiation
VCAM-1	Vascular Cell Adhesion Molecule-1
VDBP	Vitamin D Binding Protein
VDD	Vitamin D Deficiency

VDRs	Vitamin D Receptors
VDRE	Vitamin D Response Element
WHO	World Health Organization

CHAPTER I

INTRODUCTION

1.1 RESEARCH BACKGROUND

1.1.1 Global Burden of Prediabetes and Type 2 Diabetes

Prediabetes is an intermediate state of dysglycaemia characterized by impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or elevated glycated haemoglobin (HbA1c) levels below the diagnostic threshold for T2DM. The American Diabetes Association (American Diabetes Association Professional Practice 2024) defines prediabetes as fasting plasma glucose (100-125 mg/dl) 5.6–6.9 mmol/L, 2-hour postprandial (2HPP) (140-199 mg/dl) 7.8–11.0 mmol/L during an oral glucose tolerance test (OGTT), or HbA1c 5.7–6.4%. Individuals with prediabetes are at substantially increased risk of progressing to T2DM and developing cardiovascular disease. Globally, it was projected that more than one billion adults may have prediabetes by 2045 (Rooney et al. 2023), while another study emphasized its growing prevalence and future burden (Rett et al. 2019). These estimates highlight prediabetes as a major public health challenge requiring urgent preventive strategies.

T2DM is a major global public health challenge characterized by chronic hyperglycaemia due to a combination of insulin resistance and progressive pancreatic β-cell dysfunction. The condition is associated with substantial morbidity and mortality, primarily through its microvascular complications (nephropathy, retinopathy, neuropathy) and macrovascular complications (ischemic heart disease, stroke, peripheral vascular disease) (American Diabetes Association Professional Practice 2024).

According to the International Diabetes Federation (IDF, 2024), an estimated 589 million adults (20–79 years) worldwide are living with diabetes, with more than 90% of cases attributable to T2DM. Projections indicate that the number will rise to 783 million by 2045, with the greatest increases expected in low- and middle-income countries where 4 in 5 adults with diabetes currently reside. (Federation 2024).

Despite the availability of pharmacological therapies and lifestyle interventions, glycaemic control remains suboptimal worldwide. Barriers include poor adherence, limited healthcare infrastructure, and socioeconomic constraints. Consequently, T2DM continues to impose a heavy economic burden, with global health expenditure on diabetes estimated at USD 966 billion in 2021 (Federation 2024), reflecting both direct medical costs and indirect losses from disability and premature mortality.

1.1.2 Vitamin D: Biological Role and Metabolic Relevance

Vitamin D is a fat-soluble secosteroid hormone that plays a central role in calcium and phosphate homeostasis, skeletal integrity, and a wide range of extraskeletal functions. Its active metabolite, [1,25$(OH)_2$D], exerts pleiotropic effects on metabolic and vascular pathways. Through binding to the vitamin D receptor (VDR), which is expressed in pancreatic β-cells, adipocytes, skeletal muscle, vascular endothelium, and immune cells, vitamin D modulates insulin secretion, insulin sensitivity, systemic inflammatory responses, and endothelial nitric oxide production (Argano et al. 2023).

Experimental and clinical evidence further supports these mechanisms. Vitamin D enhances insulin receptor expression and regulates intracellular calcium flux, both of which are essential for insulin exocytosis. It also suppresses pro-inflammatory cytokines, including IL-6, TNF-α, and hs-CRP, thereby reducing chronic low-grade inflammation that contributes to insulin resistance and β-cell dysfunction (Guo et al. 2014). By attenuating oxidative stress and cytokine-induced apoptosis, vitamin D preserves β-cell integrity and insulin secretory capacity. In parallel, its vascular effects include stimulation of endothelial nitric oxide synthase, improved arterial compliance, and reduced endothelial activation markers, all of which contribute to enhanced vascular function and reduced cardiovascular risk. These immunometabolic actions

provide biological plausibility for the observed improvements in glycaemic indices, lipid metabolism, and endothelial health in supplementation trials, highlighting vitamin D's dual role in stabilizing glucose homeostasis and protecting vascular integrity (Olena Andrukhova, 2014).

1.1.3 Vitamin D Deficiency as a Global Health Concern

Globally, Vitamin D Deficiency (VDD) is highly prevalent, particularly in regions with limited sunlight exposure, cultural clothing practices, and dietary insufficiency (Angelino et al. 2023). It's been associated with increased risk of metabolic disorders, including prediabetes. Observational studies consistently demonstrated inverse associations between serum 25-hydroxyvitamin D [25(OH)D] concentrations and markers of glycaemic dysregulation, insulin resistance, and systemic inflammation (Cao et al. 2025; Chiu et al. 2004). VDD, especially among women and individuals with limited sun exposure, sedentary lifestyles, or poor dietary intake (Rett et al. 2019). Such findings underscore the urgent need for targeted public health interventions and highlight VDD prediabetic adults in high-risk regions as a priority population for clinical research.

1.1.4 Evidence Linking Vitamin D and Prediabetes

Meta-analyses of randomized controlled trials (RCTs) suggest that vitamin D supplementation may improve glycaemic control and reduce progression to diabetes in prediabetic individuals, but findings are heterogeneous and often limited by short intervention durations, variable dosing regimens, and inconsistent baseline vitamin D status (Molani-Gol, Rafraf, Jafarabadi, et al. 2025). These uncertainties highlight the need for rigorously designed trials in populations with endemic VDD and elevated cardiometabolic risk to clarify vitamin D's potential role as an adjunct in the prevention of diabetes.

Previous systematic reviews by Mousa et al. reported that the therapeutic efficacy of vitamin D supplementation depends on baseline deficiency, glycaemic status, and adiposity (Mousa et al. 2016). This is particularly relevant in regions such

as Yemen and Southeast Asia, where both prediabetes and hypovitaminosis D are highly prevalent due to limited sun exposure, cultural practices, and dietary insufficiency (Al-Hetar et al. 2025).

VDD, especially among women and individuals with limited sun exposure, sedentary lifestyles, or poor dietary intake (Rett et al. 2019). Such findings underscore the urgent need for targeted public health interventions and highlight VDD prediabetic adults in high-risk regions as a priority population for clinical research. A study by Lei et al, involving 294,970 participants from the UK Biobank, found that C-reactive protein (CRP) concentrations decreased sharply with increasing 25(OH)D levels in the deficiency range (<25 nmol/L), but plateaued at higher concentrations, suggesting that the anti-inflammatory effects of vitamin D are most pronounced in individuals with deficiency. (Lei et al. 2023).

Despite the biological plausibility and observational support, RCTs investigating the impact of vitamin D supplementation on glycaemic control and inflammation have yielded heterogeneous results. The SUNNY trial, a 6-month double-blind, randomized controlled trial involving 275 patients with type 2 diabetes, investigated the effect of high-dose vitamin D supplementation (50,000 IU/month) on glycemic control (Krul-Poel et al. 2014). Although supplementation successfully increased serum 25(OH)D concentrations to sufficient levels, the trial reported no significant improvements in HbA1c, fasting glucose, insulin resistance (HOMA-IR), BMI, or lipid parameters compared with placebo. Subgroup analyses in patients with baseline deficiency (<50 nmol/L) or poor glycaemic control (HbA1c >7%) similarly showed null results. These findings highlight the inconsistency of vitamin D's metabolic effects across populations and reinforce the need for context-specific studies to clarify whether vitamin D supplementation can modulate glycaemic and vascular outcomes in vulnerable groups, such as prediabetic individuals in low-resource settings. However, modest improvements in HbA1c and 2HPP were also observed in the placebo group, attenuating the magnitude of between-group differences and highlighting the influence of contextual factors such as Ramadhan fasting and spontaneous lifestyle modifications. Between groups, significant improvements were sustained only for fasting blood glucose (FBG), serum 25(OH)D, HOMA-B, and endothelial function

based on flow-mediated dilation (FMD), underscoring vitamin D's vascular benefits through nitric oxide synthesis, reduced oxidative stress, and endothelial repair. These findings parallel those of Sugden et al., who investigated the effect of a single oral dose of ergocalciferol (100,000 IU) administered over 6 weeks in vitamin D-deficient patients with T2DM. The study demonstrated significant improvements in endothelial function and reductions in systolic blood pressure, yet no meaningful changes were observed in HbA1c or insulin resistance (HOMA-IR) (Sugden et al. 2008). Taken together, the evidence strengthens the case for vitamin D optimization as a feasible, context-sensitive strategy for mitigating early metabolic dysfunction and vascular compromise in vulnerable populations. In contrast, a comprehensive meta-analysis by Cheng et al., from 39 RCTs involving 2,982 T2DM patients, demonstrated significant reductions in FBG (−0.49 mmol/L), HbA1c (−0.30%), HOMA-IR (−0.39), and fasting insulin (−1.31 μIU/mL) following vitamin D supplementation (Cheng et al. 2024). Notably, the beneficial effects were more pronounced in patients with baseline VDD, elevated HbA1c (≥8%), and higher body mass index (BMI) and in those receiving high-dose, short-duration regimens. The systematic review underscored the importance of conducting comprehensive assessments of vitamin D supplementation in relation to systemic inflammation. Subsequent systematic reviews demonstrated that supplementation produced modest reductions in hs-CRP and TNF-α, particularly among deficient populations, while findings for IL-6 and adipocytokines remained inconsistent (Mousa et al. 2016). These results emphasize the importance of subgroup analyses by baseline deficiency, dosage, and disease status, underscoring the heterogeneity of vitamin D's immunomodulatory effects.

1.2 PROBLEM STATEMENT

The escalating global prevalence of type 2 diabetes mellitus (T2DM) underscores the importance of investigating prediabetes, its precursor state, which represents a reversible stage of dysglycaemia. and a critical window for intervention. Among the modifiable risk factors, vitamin D deficiency (VDD) has emerged as a biologically plausible contributor to metabolic and vascular dysfunction. Yet, its role remains insufficiently characterized, particularly in low-resource settings (Ong et al. 2023).

In Yemen, and specifically the Ibb Governorate, the dual burden of VDD and prediabetes is compounded by geographic, cultural, and socioeconomic determinants. Meanwhile, systemic constraints within the healthcare system impede early detection and preventive measures. Despite emerging regional evidence, local data remain scarce regarding the prevalence of VDD among prediabetic individuals and the impact of supplementation on vascular and metabolic outcomes.

This doctoral study aims to investigate the association between vitamin D deficiency and prediabetes in the Ibb Governorate of Yemen. The objective is to determine whether low vitamin D levels correlate with markers of insulin resistance and inflammation, including IFG, OGTT, HbA1c, FSI, HOMA-IR, hs-CRP, and IL-6. Clarifying this association is important because it may provide valuable insights into the potential role of vitamin D supplementation in stabilizing early glycaemic dysregulation and preventing progression to T2DM.

1.3 STUDY JUSTIFICATION

Prediabetes and vitamin D deficiency represent pressing global health concerns, with particular relevance in Yemen. The rising prevalence of type 2 diabetes mellitus highlights prediabetes as a reversible stage of dysglycaemia and a critical opportunity for intervention. Vitamin D has been implicated in glycaemic regulation, insulin sensitivity, immune modulation, and lipid metabolism, yet findings remain inconsistent across populations. Evidence from the Middle East and North Africa is limited, and virtually absent for Yemen, where both prediabetes and vitamin D deficiency are highly prevalent due to environmental, cultural, and dietary determinants.

In the Ibb Governorate, this dual burden is further compounded by socioeconomic challenges and fragile healthcare infrastructure, which often result in undetected prediabetes and delayed management. Local evidence regarding the prevalence of vitamin D deficiency among individuals with prediabetes, as well as the potential benefits of supplementation on metabolic and vascular outcomes, remains scarce. This underrepresentation creates a critical knowledge gap regarding vitamin D's role in modulating cardiometabolic risk in this vulnerable population.

To bridge this knowledge gap, the study adopted a dual-phase design comprising a multicenter cross-sectional survey to quantify the prevalence of vitamin D deficiency and its associations with metabolic, inflammatory, and vascular biomarkers, followed by a randomized controlled trial evaluating the therapeutic efficacy of high-dose cholecalciferol supplementation in vitamin D-deficient prediabetic adults. Biomarkers assessed included glycaemic indices (FBS, 2HPP, HbA1c, serum insulin, HOMA-IR, HOMA-B), inflammatory markers (hs-CRP, IL-6), vascular function (FMD), lipid profile, liver and renal function, and hematological status. Recruitment across diverse healthcare centers in urban and semi-rural settings ensured demographic and socioeconomic representation, enhancing external validity.

By integrating population-level surveillance with individual-level therapeutic evaluation, this research provides region-specific evidence to inform preventive strategies, clinical guidelines, and public health policies in Yemen and similar resource-constrained MENA settings. Identifying vitamin D deficiency as a modifiable risk factor offers a pragmatic, low-cost intervention pathway that strengthens healthcare capacity, supports culturally sensitive recommendations, and advances precision public health in low-resource environments.

1.4 RESEARCH QUESTION

1.4.1 Phase 1: Cross-Sectional Study

i. What is the prevalence of prediabetes in the Ibb Governorate, Republic of Yemen?

ii. What is the prevalence of vitamin D deficiency among individuals with prediabetes?

iii. Is there an association between vitamin D deficiency and insulin resistance in prediabetes?

iv. Is there an association between vitamin D deficiency and inflammation in prediabetes?

1.4.2 Phase 2: Randomized Controlled Trial

i. Does vitamin D supplementation enhance glycemic control in prediabetic individuals, assessed through HbA1C, OGTT, and FBS?

ii. How does vitamin D supplementation influence insulin resistance in individuals with prediabetes as measured by homeostatic model assessment of insulin resistance (HOMA IR), fasting serum Insulin (FSI), and endothelial function assessment?

iii. How does vitamin D treatment impact prediabetic individuals' inflammatory markers (hsCRP and IL6)?

1.5 RESEARCH OBJECTIVES

1.5.1 General Objective

To investigate the link between vitamin D deficiency and the emergence of prediabetes, and to assess how vitamin D supplementation could influence blood sugar regulation and related health outcomes in the Ibb region of Yemen.

1.5.2 Specific Objectives

1.5.2.1 Phase 1 (Cross-sectional survey)

1. To assess the prevalence of prediabetes in the Ibb governorate in the Republic of Yemen.

2. To assess the prevalence of vitamin D deficiency among individuals with prediabetes.

3. To determine the factors associated with prediabetes (Family History of Chronic Disease, Age, Gender, and VDD)

1.5.2.2 Phase 2 (Randomized Controlled Trial)

1. To assess the impact of vitamin D supplementation on glycaemic control in individuals with prediabetes.

2. To evaluate the effect of vitamin D supplementation on insulin resistance (IR) among individuals with prediabetes, using HOMA-IR, fasting serum insulin, and endothelial function assessment.

3. To compare the effect of vitamin D supplementation on inflammatory markers (hs-CRP and IL-6) between interventional and control groups.

1.6 RESEARCH HYPOTHESES

1.6.1 Phase 1

There is an association between vitamin D deficiency and the prevalence of prediabetes in the Ibb governorate in the Republic of Yemen.

1.6.2 Phase 2

i. Vitamin D treatment will cause a significant difference in glycaemic indices as measured by FBS, serum insulin, and HbA1C, between interventional and control groups with prediabetes.

ii. Vitamin D treatment will lead to significant differences in insulin resistance, as measured by HOMA-IR, FSI, and endothelial function assessment by echo between participants in the experimental group and those in the control group with prediabetes.

iii. Vitamin D treatment will result in a significant difference in inflammatory markers (hs-CRP, IL6) between experimental and control group participants.

CHAPTER II

LITERATURE REVIEW

2.1 INTRODUCTION

The worldwide rise in prediabetes poses a significant public health challenge with serious consequences for healthcare systems, especially in low- and middle-income countries (LMICs), where structural deficiencies in healthcare infrastructure, inadequate screening measures, and insufficient preventive strategies intensify the burden of metabolic disease (Rooney et al. 2025).

Prediabetes is clinically characterized as an intermediate metabolic condition marked by IFG, IGT, or elevated HbA1c levels that remain below the diagnostic threshold for T2DM. Beyond this definition, prediabetes arises from genetic, environmental, and behavioral factors that disrupt glucose homeostasis and accelerate metabolic deterioration. The global rise in prediabetes highlights the need to understand its determinants and progression pathways (Kahn et al. 2025).

This transitory state is not simply a benign precursor, but a pathophysiological condition linked to insulin resistance, β-cell malfunction, and chronic low-grade inflammation, all of which elevate cardiometabolic risk (Lizarzaburu-Robles et al. 2024).

Prediabetes confers a substantially increased risk of both macrovascular and microvascular complications, including atherosclerosis, nephropathy, retinopathy, and neuropathy (Palladino et al. 2020). Epidemiological data demonstrate that individuals with prediabetes have a markedly elevated probability of progressing to overt diabetes

within a relatively short timeframe, often within five years if left untreated (American Diabetes Association Professional Practice 2024; Dr. Adam 2012). This trajectory underscores the critical importance of early detection and intervention. However, the asymptomatic nature of prediabetes frequently leads to a delay in diagnosis, particularly in resource-constrained settings where routine biochemical screening is limited, and public awareness remains low.

The global distribution of prediabetes reflects significant disparities, with LMICs experiencing disproportionate increases due to rapid urbanization, sedentary lifestyles, nutritional transitions, and limited access to preventive healthcare (Joseph et al. 2025). These contextual factors underscore the pressing need for population-level screening frameworks that incorporate cost-effective diagnostic tools, culturally tailored health education, and community-based interventions. Furthermore, identifying and modifying risk factors such as obesity, physical inactivity, micronutrient deficiencies, and dietary imbalances is essential to curbing disease progression and mitigating long-term complications. From a public health perspective, strengthening surveillance systems, enhancing primary care capacity, and embedding preventive strategies into national health policies are indispensable steps toward addressing the escalating burden of prediabetes and its downstream consequences (Merve Belenli 2025).

Among emerging metabolic determinants, VDD has garnered considerable attention for its potential role in the pathogenesis of insulin resistance and cardiometabolic dysfunction. Traditionally, vitamin D has been recognised for its role in calcium-phosphorus homeostasis and skeletal integrity. It's now understood to exert pleiotropic effects through its nuclear receptor-mediated actions in various tissues, including pancreatic β-cells, adipocytes, vascular endothelium, and immune cells (Bouillon 2008; Muscogiuri 2017). A previous study demonstrated that vitamin D affects insulin secretion by modulating intracellular calcium signalling in β-cells, enhances insulin sensitivity by upregulating insulin receptor expression, and attenuates chronic low-grade inflammation by suppressing pro-inflammatory cytokines such as IL-6 and TNF-α (Ul Islam Hashmi et al. 2025).

This finding aligns with epidemiological studies indicating inverse associations between serum 25-hydroxyvitamin D [25(OH)D] concentrations and glycaemic indices, including FBS, HbA1c, and HOMA-IR (Anastassios G. Pittas 2019; Shoaib Afzal 2013).

Furthermore, VDD has been associated with endothelial dysfunction, a precursor to atherosclerosis and cardiovascular disease, through its effects on nitric oxide bioavailability, oxidative stress, and vascular smooth muscle cell proliferation. Flow-mediated dilation (FMD), an established non-invasive assessment of endothelial function, has been shown to improve following vitamin D repletion in vitamin D-deficient individuals, suggesting a potential vascular-protective role (Yuen-Fung 2013).

In the MENA region, VDD is highly prevalent due to a confluence of environmental, cultural, and dietary factors (Hassan et al. 2025). Limited ultraviolet B (UVB) exposure resulting from conservative clothing practices, indoor lifestyles, and high atmospheric pollution levels contributes to inadequate cutaneous vitamin D synthesis. Additionally, low dietary intake of vitamin D-rich foods and limited fortification policies exacerbate the burden of VDD (Al-Daghri et al. 2015). Yemen, and specifically the Ibb Governorate, presents a unique epidemiological context where high-altitude geography, widespread nutritional insufficiencies, and constrained healthcare access converge to amplify both VDD and prediabetes risk. Despite this, there remains a paucity of region-specific data exploring the intersection of these conditions, limiting the development of culturally and contextually appropriate interventions (Al-Hetar Mamy 2024).

Intervention studies have increasingly examined the therapeutic potential of vitamin D supplementation in prediabetic populations. Randomized controlled trials demonstrate that high-dose vitamin D_3 administration can enhance insulin sensitivity, improve lipid profiles, and reduce systemic inflammatory markers (Bruna-Mejías et al. 2025). Despite these promising findings, results remain heterogeneous, with variability largely attributable to differences in baseline deficiency status, dosage regimens, supplementation duration, and population characteristics. Meta-analyses confirm that individuals with severe baseline deficiency derive the greatest metabolic benefit,

underscoring the importance of stratified intervention strategies tailored to initial vitamin D status (Mirhosseini et al. 2018).

Beyond metabolic regulation, the interplay between vitamin D status and vascular health has gained prominence in recent literature. Endothelial dysfunction, frequently observed in the early stages of prediabetes, is a well-established predictor of future cardiovascular events. Vitamin D has been shown to restore endothelial integrity through anti-inflammatory and antioxidative mechanisms, thereby improving flow-mediated dilation and reducing vascular risk (Gyuri 2024). These dual effects position vitamin D as a promising adjunct in cardiometabolic risk-reduction strategies, particularly in populations with elevated baseline risk and limited access to pharmacological interventions (Pilz et al. 2016).

Globally, the high prevalence of both prediabetes and VDD represents a significant and underappreciated public health challenge. Prediabetes, as an intermediate metabolic state, predisposes individuals to T2DM and its associated complications, while VDD has been increasingly implicated in impaired glucose metabolism, endothelial dysfunction, and heightened cardiometabolic risk (Kretschmer et al. 2025).

Regional data from Yemen and the broader MENA confirm alarmingly high rates of VDD, with cross-sectional studies reporting prevalence exceeding 70% in adults (Al-Hetar Mamy 2024; Lotfi Saeed Bin Dahman 2020). The coexistence of these conditions underscores the urgent need for integrated epidemiological and interventional research.

Despite growing evidence from RCTs and meta-analyses showing that vitamin D supplementation can improve β-cell function, insulin sensitivity, and vascular outcomes, data remain scarce in resource-limited settings such as Yemen. This gap highlights the importance of situating Yemen within the broader landscape of metabolic health disparities and justifies further investigation into the cardiometabolic role of vitamin D in populations with endemic deficiency.

2.2 PREDIABETES: DEFINITION AND DIAGNOSTIC CRITERIA

Prediabetes is defined as an intermediate metabolic state between normoglycemia and T2DM, characterized by subclinical disturbances in glucose regulation that fall below diagnostic thresholds for overt diabetes. It reflects a continuum of metabolic dysfunction involving impaired insulin sensitivity, β-cell dysfunction, and postprandial hyperglycaemia, and is associated with increased risk of progression to T2DM as well as cardiovascular and microvascular complications (American Diabetes Association Professional Practice 2024).

2.2.1 Diagnostic Thresholds

Prediabetes was defined according to the American Diabetes Association (ADA) Standards. Diagnosis required the presence of at least one of the following criteria: (1) impaired fasting glucose (FPG 100–125 mg/dL; 5.6–6.9 mmol/L); (2) impaired glucose tolerance (2-hour plasma glucose 140–199 mg/dL; 7.8–11.0 mmol/L) following a 75 g oral glucose tolerance test (OGTT); or (3) elevated glycated hemoglobin (HbA1c 5.7–6.4%). HbA1c reflects average glycemia over 2–3 months, whereas FPG and OGTT measure immediate plasma glucose levels. Individuals meeting any one of these criteria were classified as having prediabetes (ADA, 2025).

Table 2.1 Criteria defining pre-diabetes

GLYCEMIC INDICES	WHO	ADA
Impaired Fasting Glucose (mmol/L)	6.1 - 6.9	5.6 - 6.9
Impaired Glucose Tolerance (mmol/L) (2 HPP after Ingesting 75 g Oral Glucose	7.8-11.0	7.8 -11.0
HbA1c (%)		5.7-6.4

These thresholds are derived from epidemiological evidence linking intermediate glycaemic ranges to heightened risk of diabetes, CVD, and microvascular complications (American Diabetes 2025; World Health 2006). The ADA recommends screening for prediabetes in all adults aged ≥35 years, and in younger individuals with overweight or obesity (BMI ≥25 kg/m², or ≥23 kg/m² in Asian populations) who present additional risk factors such as hypertension, dyslipidemia, family history of diabetes, or prior gestational diabetes mellitus (GDM).

WHO adopts similar thresholds but emphasizes the OGTT as the diagnostic gold standard, particularly in populations with high postprandial glycaemic excursions (World Health 2006). In resource-limited settings, FBG or HbA1c may be more feasible, though these tests risk underdiagnosing certain dysglycaemic phenotypes.

Despite broad consensus, subtle differences in diagnostic criteria across organizations contribute to variability in prevalence estimates and clinical decision-making. HbA1c-based diagnosis may be confounded by haemoglobinopathies, anaemia, or altered erythrocyte turnover, which are prevalent in specific ethnic groups. Conversely, OGTT offers superior sensitivity but is logistically demanding and less practical for large-scale screening (Budak et al. 2026).

Emerging research suggests that integrating non-glycaemic indicators such as insulin resistance indices (e.g., HOMA-IR), inflammatory biomarkers (e.g., IL-6, hs-CRP), and endothelial function parameters (e.g., FMD) may enhance risk stratification and provide a more comprehensive assessment of cardiometabolic risk (Gyuri 2024). Such multidimensional approaches are particularly relevant in research contexts and may inform future revisions of diagnostic guidelines.

2.3 GLOBAL AND REGIONAL EPIDEMIOLOGY OF PREDIABETES

2.3.1 Global Prevalence Trends

Prediabetes is increasingly recognized as a “silent epidemic” due to its asymptomatic nature and high risk of progression to type 2 diabetes mellitus (T2DM). Globally, an estimated 541 million adults currently live with prediabetes, with projections rising to 730 million by 2050 (Rooney et al. 2023). Aging populations drive this growth, urbanization, reduced physical activity, and dietary shifts toward processed, calorie-dense foods (Pan et al. 2025).

In high-income countries, prevalence is striking. In the United States, the CDC reports over 115 million adults (≈45%) with prediabetes, disproportionately affecting older adults (≈50% of those ≥65 years), Hispanic and non-Hispanic Black populations,

and individuals with obesity or metabolic syndrome (CDC 2026). In China**,** national surveys estimate 35–38% prevalence, largely linked to industrialization, urban migration, and dietary changes (Xie et al. 2022).

In India, prevalence ranges from 10–14%**,** with clear urban–rural disparities: urban centers show higher rates due to sedentary lifestyles and dietary westernization, while rural populations face underdiagnosis and limited screening access (Anjana et al. 2020). Across South Asia, systematic reviews confirm similar patterns, with metropolitan regions showing elevated rates and wide variation reflecting socioeconomic diversity and uneven healthcare access (Ali et al. 2025).

2.3.2 Prediabetes in MENA

Epidemiological data in the Middle East and North Africa (MENA) remain fragmented, yet studies consistently show rising prediabetes prevalence, closely linked to obesity, physical inactivity, and vitamin D deficiency (Assaad Khalil et al. 2019). Cultural dietary patterns rich in refined grains and sugars, limited sun exposure, and genetic predisposition contribute to early metabolic derangements. In Yemen, the dual burden of undernutrition and emerging non-communicable diseases is compounded by fragile healthcare infrastructure and humanitarian challenges, underscoring the need for context-sensitive interventions (Médecins Sans Frontières 2025; UNICEF 2025).

Community-based surveys in Egypt estimate the prevalence of prediabetes at ~20%, particularly in metropolitan areas such as Cairo and Alexandria (Farag et al. 2023). In Jordan, national studies report rising rates of IFG and prediabetes, especially in urban centers (Omar Abu Hijleh et al. 2021). In Kuwait, prevalence exceeds 20%, driven by lifestyle transitions toward processed foods and reduced physical activity (Alkandari et al. 2020). These findings highlight a consistent regional pattern: urban populations across MENA show higher prevalence than rural counterparts, reflecting obesity, inactivity, and dietary westernization.

Compounding this burden is the widespread prevalence of vitamin D deficiency (VDD), endemic in MENA due to limited UVB exposure, conservative clothing

practices, indoor lifestyles, pollution, and low dietary intake. This paradox of "sun-rich but vitamin D-poor" populations (Riam 2025) is clinically significant, as VDD exacerbates insulin resistance, impairs β-cell function, and promotes endothelial dysfunction, accelerating prediabetes and vascular complications (Rasouli et al. 2022).

The International Diabetes Federation (IDF) identifies MENA as one of the fastest-growing regions for diabetes and prediabetes. Projections indicate a 92% increase in adults with diabetes, from 85 million in 2024 to 163 million by 2050, the second-highest regional rise globally. Alarmingly, one in three adults remains undiagnosed, reflecting major gaps in screening and health system responsiveness (IDF 2025).

In summary, MENA faces a dual epidemic of prediabetes and VDD, driven by rapid lifestyle transitions and systemic healthcare limitations. Integrating micronutrient assessment and targeted supplementation into metabolic risk screening may provide a pragmatic, culturally sensitive approach to mitigating the rising cardiometabolic burden

2.3.3 Prediabetes in Yemen

Prediabetes is an emerging public health challenge in Yemen, where surveillance of non-communicable diseases (NCDs) is fragmented and under-resourced. Although national data are limited, available studies suggest a moderate to high prevalence of dysglycaemia, particularly in urban centers, with the true burden likely underestimated due to weak diagnostic infrastructure and low public awareness (Alrubaiee 2025).

A cross-sectional study in Sana'a reported a prediabetes prevalence of 16.2% among adults aged 20–60 years, based solely on FPG (Al-Sharafi et al. 2021). Similarly, a semi-rural survey near Sana'a found an age-standardized prevalence of 9.0% for IFG or IGT, alongside diabetes (10.4%) and hypertension (14.2%) (Gunaid et al. 2008). Age and central obesity were identified as key predictors of glucose intolerance, underscoring lifestyle and dietary risk factors. These findings, however, likely underestimate national prevalence due to limited geographic coverage, small sample sizes, and reliance on IFG alone, which may miss isolated IGT.

The Ibb Governorate presents a distinct epidemiological profile shaped by altitude, climate, and socioeconomic conditions. Nutritional deficiencies, particularly VDD, are widespread due to reduced UVB exposure, dietary inadequacies, and cultural practices. VDD may exacerbate insulin resistance and endothelial dysfunction, compounding metabolic risk alongside physical inactivity, dietary transitions, and socioeconomic instability (Al-Hetar Mamy 2024). Yet no multicenter study has quantified the prevalence of prediabetes in Ibb, thereby limiting targeted interventions.

2.4 RISK FACTORS AND PROGRESSION OF T2DM

Risk factors for T2DM can be broadly categorized into non-modifiable and modifiable domains. Non-modifiable risks include age, family history, genetic predisposition, and ethnicity. Advancing age is associated with reduced insulin sensitivity and declining β-cell function, which together increase susceptibility to hyperglycemia (Idf 2025).

2.4.1 Non-Modifiable Risk Factors

Non-modifiable risk factors represent inherent biological and genetic determinants that predispose individuals to type 2 diabetes and cannot be altered through lifestyle or medical intervention. Advancing age is a critical determinant, as progressive decline in β-cell function and reduced insulin sensitivity contribute to the rising incidence of diabetes observed after midlife (Abbas 2022). Family history and genetic predisposition further elevate risk, with shared genetic variants such as *TCF7L2, PPARG*, and *FTO* strongly associated with impaired insulin secretion, obesity, and insulin resistance (Abbas 2022).

Ethnic background also plays a significant role, with Middle Eastern, South Asian, and African populations demonstrating heightened susceptibility to insulin resistance and earlier onset of diabetes, often at lower BMI thresholds compared to Caucasian populations. These disparities reflect differences in visceral adiposity, muscle composition, and genetic polymorphisms (Alkandari et al. 2020). Sex and reproductive history contribute distinct trajectories: women with a history of gestational diabetes are at substantially increased risk of developing type 2 diabetes later in life,

while men with central adiposity exhibit a different but equally significant risk profile (Alkandari et al. 2020).

Finally, epigenetic programming exerts long-term influence, as intrauterine exposure to maternal hyperglycemia predisposes offspring to early insulin resistance and metabolic dysfunction, reinforcing the intergenerational transmission of diabetes risk (Abbas 2022). Collectively, these non-modifiable factors underscore the importance of early identification and targeted preventive strategies in high-risk populations.

2.4.2 Modifiable Risk Factors

Finally, epigenetic programming exerts long-term influence, as intrauterine exposure to maternal hyperglycemia predisposes offspring to early insulin resistance and metabolic dysfunction, reinforcing the intergenerational transmission of diabetes risk (Merve Belenli 2025). A sedentary lifestyle reduces skeletal muscle glucose uptake and impairs mitochondrial function, whereas regular physical activity enhances insulin signaling and glycaemic control (Małkowska 2024). Unhealthy dietary patterns rich in refined carbohydrates, saturated fats, and sugars promote hyperglycemia, lipotoxicity, and oxidative stress, while low intake of fiber, whole grains, and micronutrients reduces insulin sensitivity and β-cell resilience (Dansinger et al. 2025). In contrast, protective dietary models such as the Mediterranean and plant-based diets exert anti-inflammatory effects, improve insulin sensitivity, and consistently reduce progression to T2DM (Martín-Peláez et al. 2020).

Sleep disturbances, including short sleep duration and poor sleep quality, exacerbate insulin resistance through cortisol dysregulation and sympathetic activation (Mao et al. 2024). Psychosocial stress and depression elevate cortisol and catecholamines, impairing insulin signaling and increasing metabolic risk (Brooks et al. 2025). Lifestyle behaviors such as tobacco and alcohol use further compound risk through oxidative stress, hepatic dysfunction, and endothelial damage (Aruna D. Pradhan et al. 2001; Steiner et al. 2015).

Beyond lifestyle, environmental exposures such as chronic air pollution (PM2.5, traffic-related pollutants) promote systemic inflammation, oxidative stress, and endothelial dysfunction, thereby increasing the risk of diabetes (Rajagopalan et al. 2012). Chronic inflammatory conditions, including periodontal disease and persistent infections, contribute to low-grade systemic inflammation, which interferes with insulin receptor signaling and accelerates metabolic deterioration (Ranbhise et al. 2025).

Finally, micronutrient deficiencies are increasingly recognized as modifiable risks. Vitamin D deficiency impairs both insulin secretion and peripheral sensitivity, contributing to dysglycaemia and increased diabetes risk (Sabia et al. 2022). Magnesium deficiency disrupts insulin receptor phosphorylation and glucose transport, worsening insulin resistance (Razzaque et al. 2025). Vitamin B12 deficiency, often medication-induced through long-term metformin therapy, exacerbates metabolic risk by impairing glucose metabolism and elevating homocysteine (Martianto et al. 2021). Zinc deficiency compromises insulin synthesis, storage, and secretion, and increases oxidative stress and β-cell dysfunction (Bleizgys 2024). Similarly, chromium deficiency reduces insulin sensitivity and glucose uptake, promoting hyperglycaemia and accelerating progression to diabetes (Elegbeleye et al. 2025).

Pharmacological exposures also represent modifiable risks. Long-term use of glucocorticoids, atypical antipsychotics, and thiazide diuretics is associated with hyperglycaemia and drug-induced diabetes, underscoring the need for careful monitoring of glycaemic status in patients receiving these therapies (Kokkinopoulou et al. 2021). Collectively, these factors demonstrate the multifaceted nature of modifiable risk, encompassing lifestyle and diet, psychosocial stressors, chronic inflammation, and medication use. Addressing them through integrated preventive strategies is essential to reducing the burden of diabetes in at-risk populations.

2.4.3 Natural History of Prediabetes

Prediabetes reflects a dual defect of insulin resistance and β-cell dysfunction. Insulin resistance in hepatic and peripheral tissues impairs glucose uptake and increases hepatic glucose production, thereby elevating fasting and postprandial glucose. Initially, β cells

compensate by hypersecreting insulin, but this adaptation fails due to glucotoxicity, lipotoxicity, oxidative stress, and endoplasmic reticulum stress, leading to progressive exhaustion. Amyloid deposition and mitochondrial dysfunction further impair insulin production (Bkaily et al. 2025). Chronic low-grade inflammation, with elevated IL-6 and hs CRP, predicts progression to T2DM and contributes to endothelial dysfunction. Oxidative stress from reactive oxygen species impairs insulin signaling and accelerates cellular damage (Pellegrini et al. 2024). Emerging evidence also implicates gut microbiota dysbiosis, which alters short-chain fatty acid production and promotes systemic inflammation, linking intestinal health to metabolic risk.

Vascular abnormalities are common in prediabetes. Endothelial dysfunction, reduced nitric oxide bioavailability, and vascular inflammation compromise vascular integrity and promote atherogenesis. Arterial stiffness and microvascular dysfunction are early features, while dyslipidemia, characterized by high triglycerides, low HDL, and small dense LDL particles, accelerates plaque formation and increases cardiovascular risk (Yudkin et al. 1999). Subclinical markers such as carotid intima media thickness and coronary calcium scores highlight the systemic nature of prediabetes beyond glycemia.

2.4.4 Prevention Strategies

Progression trajectories vary considerably. Some individuals achieve normoglycemia through lifestyle changes, others remain stable, while a subset progresses rapidly to T2DM or develops complications despite apparently stable indices. Screening instruments such as FINDRISC and the ADA risk score facilitate the identification of individuals as most susceptible to developing diabetes. Landmark trials, including the Diabetes Prevention Program (DPP) and the Finnish Diabetes Prevention Study (DPS), demonstrated that intensive lifestyle modification, dietary changes, increased physical activity, and weight reduction reduced T2DM incidence by approximately 58% over three years, with sustained benefits over a decade (Jaana LindströM et al. 2003).

Pharmacological interventions have also demonstrated benefit. In the Diabetes Prevention Program (2002), metformin reduced progression to type 2 diabetes by

approximately 31%, with the greatest effect observed among younger obese individuals and women with prior gestational diabetes (Diabetes Prevention Program Research Group, 2002).

Other agents, such as thiazolidinediones and α-glucosidase inhibitors, offer modest effects but are limited by side effects and cost. More recently, GLP-1 receptor agonists and SGLT2 inhibitors have emerged as promising preventive therapies, with added cardiovascular benefits (Avogaro A 2026).

Vitamin D supplementation has gained attention as a potential adjunct in reducing progression to T2DM. Evidence suggests improvements in insulin sensitivity, β-cell function, and endothelial health (Krisnamurti et al. 2023). Vitamin D modulates calcium flux in β cells, enhances insulin receptor expression, and exerts anti-inflammatory effects, while genetic variations in vitamin D receptor polymorphisms may influence individual responsiveness (Tarfeen et al. 2022). These findings position vitamin D as a promising candidate for metabolic intervention, complementing established lifestyle and pharmacological strategies.

2.5 VITAMIN D PHYSIOLOGY AND MOLECULAR MECHANISMS

2.5.1 Synthesis and Metabolism

Vitamin D is a pleiotropic secosteroid hormone with roles extending beyond calcium–phosphorus homeostasis and skeletal integrity. It regulates mineral balance, immune responses, cellular proliferation, and endocrine pathways (Bouillon et al. 2019; Christakos et al. 2016). Cutaneous exposure to UVB converts 7-dehydrocholesterol into cholecalciferol (vitamin D_3), which undergoes hepatic hydroxylation to 25-hydroxyvitamin D [25(OH)D], the major circulating biomarker. Renal hydroxylation by CYP27B1 produces 1,25-dihydroxyvitamin D [$1,25(OH)_2D_3$], the active metabolite responsible for systemic actions.

2.5.2 Genomic and Non-Genomic Actions

Vitamin D acts through both genomic and non-genomic pathways. Genomically, $1,25(OH)_2D_3$ binds to the vitamin D receptor (VDR), expressed in >30 tissues, forming a heterodimer with RXR that regulates genes involved in calcium transport, insulin secretion, immune modulation, and cell cycle control (Voltan et al. 2023). Non-genomic actions, mediated via membrane-bound VDRs, rapidly influence calcium flux, kinase activation, and oxidative stress (Żmijewski 2022).

Globally, vitamin D deficiency (VDD) affects ~1 billion people (Abbas 2022; Holick 2007). VDD is associated with type 2 diabetes, cardiovascular disease, autoimmune disorders, neurodegeneration, and cancers, largely through impaired insulin sensitivity, reduced β-cell function, and chronic inflammation (Młynarska et al. 2025). In MENA, prevalence is particularly high due to clothing norms, indoor lifestyles, pollution, and limited fortification. In Yemen's Ibb Governorate, high altitude, poor diet, and weak healthcare infrastructure intensify the burden, making VDD a modifiable risk factor with major public health implications (Al-Hetar Mamy 2024)

2.6 ETIOLOGY AND DETERMINANTS OF VITAMIN DEFICIENCY

2.6.1 Environmental Determinants

Sunlight exposure is the primary determinant of endogenous vitamin D synthesis, as UVB radiation converts 7-dehydrocholesterol in the skin into previtamin D3, which then undergoes thermal isomerization to form vitamin D3; excess exposure is self-regulated through photodegradation into inert metabolites, preventing toxicity (Voiculescu et al. 2025). The efficiency of this process is influenced by latitude, season, climate, air pollution, skin pigmentation, age, and cultural practices such as veiling or deliberate sun avoidance (Anoop Mithal et al. 2009; Cashman et al. 2016). These modifiers explain the paradox of widespread deficiency in sun-rich regions like the Middle East and Southeast Asia, where behavioral and cultural factors outweigh environmental availability (Neville et al. 2021). Clinical evidence links inadequate

sunlight exposure to low serum 25(OH)D, insulin resistance, impaired β-cell function, and endothelial dysfunction, connecting environmental determinants to metabolic risk (Kayaniyil et al. 2010). While sunlight is a recognized determinant, this study assessed vitamin D status using biochemical markers and the effects of supplementation, providing objective and reproducible measures of deficiency and its metabolic consequences (Giustina et al. 2024).

2.6.2 Behavioral and Sociocultural Determinants

Behavioral and sociocultural determinants play a critical role in shaping vitamin D status, often overriding environmental availability of sunlight. Conservative clothing and veiling substantially reduce dermal exposure to UVB radiation, particularly among women in certain communities, while indoor lifestyles driven by urbanization, occupational patterns, and recreational habits further limit opportunities for cutaneous synthesis (Sylvester 2022). Gender-based restrictions on outdoor activity compound this risk, as women in some societies spend less time outdoors compared to men, intensifying vulnerability to hypovitaminosis D. These factors explain why deficiency remains highly prevalent even in sun-rich regions, underscoring the need to contextualize vitamin D deficiency within broader societal and cultural frameworks that intersect with biological and environmental determinants.

2.6.3 Nutritional Determinants

Dietary insufficiency remains a critical extrinsic determinant of VDD. Natural food sources of vitamin D, such as fatty fish, egg yolks, and fortified dairy products, are often limited or inaccessible in low and middle-income countries (LMICs), where socioeconomic and cultural factors constrain dietary diversity (Pamela Mason* 2023). In many LMICs, food fortification policies are either absent or inconsistently implemented, contributing to widespread subclinical deficiency despite global evidence supporting fortification as a sustainable public health strategy (Alnafisah et al. 2024).

2.6.4 Pharmacological and Clinical Determinants

Pharmacological interventions represent an additional determinant of vitamin D status. Prolonged administration of anticonvulsants (such as phenytoin and carbamazepine), glucocorticoids, and antiretroviral agents accelerates vitamin D catabolism or disrupts its enzymatic activation, thereby heightening the risk of deficiency (Giustina et al. 2023). These drug-nutrient interactions are particularly relevant in patients with chronic neurological, autoimmune, or infectious diseases, where pharmacotherapy is prolonged, and the risk of deficiency is heightened.

2.7 GLOBAL AND REGIONAL BURDEN OF VITAMIN D DEFICIENCY

2.7.1 Global Overview

Vitamin D deficiency (VDD) is a paradoxical public health challenge across the Middle East and North Africa (MENA). Despite abundant sunlight, hypovitaminosis D remains highly prevalent due to environmental, behavioral, nutritional, and sociocultural factors. Its impact extends beyond skeletal health to immune regulation, insulin sensitivity, endothelial function, and chronic disease risk (Pludowski et al. 2022). In Yemen, systemic instability, food insecurity, and weak healthcare infrastructure magnify these challenges, particularly in high-altitude regions such as Ibb.

2.7.2 MENA Paradox

Population studies consistently report VDD rates exceeding 50–80% across MENA, especially among women, adolescents, and urban residents (Al-Ajlan et al. 2023; Al-Hetar Mamy 2024; Bassil et al. 2013). In Saudi Arabia, >80% of adults had serum 25(OH)D <20 ng/mL (Hwalla et al. 2017). Similar findings are documented in the UAE, Qatar, Jordan, and Lebanon, where cultural dress codes, reduced outdoor mobility, and limited dietary diversity drive deficiency (Nassar et al. 2021). Gender disparities are striking; women face restricted UVB exposure and limited nutritional autonomy, while adolescent girls show high deficiency rates due to indoor schooling and poor diet (Alblooshi et al. 2023). Urbanization further exacerbates risks by promoting indoor lifestyles and reducing incidental sun exposure.

The persistence of VDD in sun-rich countries reflects environmental and sociocultural barriers to UVB synthesis. Conservative clothing, indoor work, and avoidance of outdoor activity during peak heat limit dermal exposure (Hwalla et al. 2017). Dietary intake is inadequate, as vitamin D-rich foods (fatty fish, liver, egg yolks) are rarely consumed in sufficient amounts. Fortification policies remain inconsistent, with limited access in rural and low-income settings (Anoop Mithal et al. 2009). Public awareness of vitamin D's systemic roles is low, screening is rarely integrated into primary care, and access to supplementation is limited. The absence of national guidelines further compounds the burden of deficiency.

2.7.3 Vitamin D Deficiency in Yemen

VDD in Yemen represents a paradoxical yet pressing public health concern. Population-based studies and RCTs consistently demonstrate high prevalence rates. Reports from Sana'a and Ibb indicate a deficiency exceeding 70% among women and adolescents, with mean serum 25(OH)D often <20 ng/mL (Alwabr et al. 2020). These findings align with regional reviews across MENA, which highlight Yemen as part of the broader paradox of sun-rich countries with persistently high VDD due to environmental, sociocultural, and nutritional determinants (Al-Hetar MAMY, 2024). Gender disparities in VDD are acute across the Middle East, North Africa (MENA), and globally. Women are disproportionately affected due to sociocultural determinants such as conservative clothing that restricts ultraviolet B (UVB) exposure, reduced outdoor activity, and limited nutritional autonomy (Bedewy et al. 2022). Adolescents, particularly girls, also exhibit high deficiency rates driven by indoor schooling, sedentary lifestyles, and poor dietary diversity. Cultural and behavioral practices intensify systemic barriers imposed by conflict, instability, and socioeconomic hardship, driving pervasive deficiency across all demographic groups.

2.8 VITAMIN D AND GLUCOSE HOMEOSTASIS

2.8.1 Pancreatic β-Cell Function

Pancreatic β-cells regulate glucose homeostasis through insulin secretion, a process initiated by glucose metabolism that increases the ATP/ADP ratio, closes ATP-sensitive

potassium channels, depolarizes the membrane, and opens voltage-dependent calcium channels. The resulting calcium influx triggers exocytosis of insulin granules (Henquin 2000).

Vitamin D enhances β-cell function via genomic regulation of insulin transcription (PDX-1, MafA) and stabilization of calcium-dependent exocytosis (Maestro et al. 2000). Deficiency impairs glucose-stimulated insulin secretion, while supplementation restores activity (Fuentes-Barría et al. 2025). Clinical evidence supports β-cell preservation as a cornerstone of metabolic health, with RCTs showing improved fasting plasma glucose, oral glucose tolerance, triglycerides, and endothelial function (Afraie et al. 2024).

2.8.2 Peripheral Insulin Sensitivity

Peripheral insulin sensitivity refers to the responsiveness of skeletal muscle, adipose tissue, and liver to circulating insulin. The binding of insulin to its receptor activates PI3K/Akt signaling, promoting GLUT4 translocation to the plasma membrane and facilitating glucose uptake (Satoh 2014). AMPK activation enhances glucose uptake and fatty acid oxidation, improving metabolic flexibility (Hardie et al. 2012). Vitamin D improves insulin sensitivity through AMPK activation, GLUT4 translocation, and insulin receptor regulation (Fuentes-Barría et al. 2025).

Deficiency promotes inflammation via IL-6, TNF-α, and CRP, impairing insulin signaling (Argano et al. 2025). Observational studies confirm inverse correlations between 25(OH)D and FPG, HbA1c, and HOMA-IR (Bruna-Mejías et al. 2025). Supplementation improves glycemic indices and endothelial function (Jennifer C. Seida 2014).

2.9 VITAMIN D AND INFLAMMATORY MODULATION

Chronic low-grade inflammation is increasingly recognized as a central mechanism linking metabolic dysfunction to the progression of prediabetes and type 2 diabetes mellitus. Pro-inflammatory cytokines such as IL-6 and TNF-α impair insulin signaling

by activating stress kinases (e.g., JNK, IKKβ) that phosphorylate insulin receptor substrates at inhibitory sites, thereby reducing downstream PI3K/Akt signaling. This results in diminished glucose uptake in skeletal muscle and adipose tissue and impaired suppression of hepatic gluconeogenesis (Acosta-Martinez et al. 2022).

The transcription factor nuclear factor-κB (NF-κB) plays a pivotal role in this immune-metabolic crosstalk. NF-κB activation in adipose tissue macrophages and pancreatic islets promotes the release of pro-inflammatory mediators, exacerbating insulin resistance and contributing to β-cell stress and apoptosis. Conversely, anti-inflammatory cytokines such as IL-10 counterbalance these effects by inhibiting NF-κB signaling and restoring insulin sensitivity. Vitamin D has been shown to modulate these pathways by suppressing NF-κB activation, reducing IL-6 and TNF-α secretion, and enhancing IL-10 production. Through these immunomodulatory effects, vitamin D improves insulin signaling, preserves β-cell function, and reduces systemic metabolic stress (Jeffery et al. 2016). Observational studies consistently report inverse associations between circulating 25-hydroxyvitamin D [25(OH)D] levels and markers of insulin resistance, including HOMA-IR and fasting plasma glucose. Randomized controlled trials further confirm that vitamin D supplementation in deficient individuals improves glycaemic indices, reduces inflammatory markers, and enhances cardiometabolic profiles (Kahn et al. 2025).

This immune-metabolic crosstalk underscores the importance of considering inflammation not only as a consequence of metabolic dysfunction but also as a driver of disease progression. Vitamin D, by intersecting immunological and metabolic pathways, functions as a therapeutic modulator that mitigates inflammation, enhances insulin sensitivity, and delays progression from prediabetes to overt diabetes.

2.10 VITAMIN D AND VASCULAR FUNCTION (ENDOTHELIAL DYSFUNCTION)

Vitamin D deficiency is closely associated with endothelial dysfunction, a key early event in the pathogenesis of cardiovascular disease. Endothelial cells express vitamin D receptors (VDRs), and activation by $1,25(OH)_2D$ improves endothelial integrity by reducing oxidative stress and inflammation. Deficiency, conversely, promotes vascular

inflammation, impairs endothelial repair, and accelerates arterial stiffness (Kim et al. 2020).

NO bioavailability is central to vascular homeostasis. Vitamin D enhances endothelial nitric oxide synthase (eNOS) activity, thereby increasing NO production and improving vasodilation. Deficiency reduces NO bioavailability, contributing to impaired vascular tone and increased risk of hypertension and atherosclerosis (Wolf et al. 2020).

FMD is a clinical marker of endothelial function. Randomized controlled trials and observational studies demonstrate that vitamin D supplementation improves FMD in deficient individuals, reflecting enhanced endothelial responsiveness and reduced vascular inflammation (Młynarska et al. 2025). These improvements highlight vitamin D's role in maintaining vascular elasticity and reducing cardiovascular risk.

Vitamin D deficiency contributes to atherosclerosis progression through multiple mechanisms: dysregulated lipid metabolism, chronic inflammation, and endothelial dysfunction. Vitamin D modulates lipid profiles, reduces pro-atherogenic cytokines, and inhibits vascular smooth muscle proliferation, thereby slowing plaque formation (Surdu et al. 2021). Epidemiological evidence links low serum 25(OH)D levels with increased incidence of coronary artery disease and adverse cardiovascular outcomes.

2.11 VITAMIN D AND LIPID METABOLISM

Vitamin D has emerged as a potential modulator of lipid metabolism through its genomic and non-genomic actions. The active form [$1,25(OH)_2D_3$] binds to the vitamin D receptor (VDR), which is expressed in hepatocytes, adipocytes, and vascular endothelial cells. Upon activation, VDR regulates the transcription of genes involved in lipid synthesis, transport, and clearance, including sterol regulatory element-binding proteins (SREBPs), apolipoproteins (e.g., ApoA1, ApoB), and apolipoproteins (e.g., ApoA1, ApoB), and lipoprotein lipase (LPL) (Surdu et al. 2021). These changes promote healthier lipid parameters and help limit hepatic steatosis.

Previous studies have demonstrated that vitamin D supplementation may attenuate hepatic lipid accumulation, reduce LDL-C and TG levels, and enhance HDL-C, particularly in individuals with metabolic syndrome or NAFLD. Mechanistically, vitamin D acts through VDR-mediated regulation of lipid metabolism, influencing PPAR pathways and reducing hepatic steatosis by modulating fatty acid oxidation and lipogenesis. Clinical evidence supports these effects: a systematic review and meta-analysis of RCTs found that vitamin D supplementation significantly improved lipid profiles in adults with metabolic syndrome, with reductions in LDL-C and TG and increases in HDL-C (Alanouti et al. 2020). Another meta-analysis confirmed that vitamin D supplementation exerts beneficial effects on lipid metabolism and cardiometabolic risk factors, though the magnitude of improvement varies depending on baseline vitamin D status and study population (Federico Ravaioli, 2022). These findings suggest that vitamin D supplementation may provide adjunctive benefits in managing metabolic syndrome and NAFLD, although long-term outcomes and dose-response relationships require further investigation.

A recent meta-analysis demonstrated that vitamin D supplementation significantly improved lipid parameters and reduced markers of hepatic inflammation in patients with obesity-associated metabolic syndrome. These benefits were attributed to improved insulin sensitivity, reduced hepatic steatosis, and enhanced endothelial function (Ge et al. 2025).

Vitamin D also modulates systemic inflammation, which plays a pivotal role in lipid metabolism and atherogenesis. VDD is associated with elevated levels of pro-inflammatory cytokines such as IL-6, TNF-α, and CRP, all of which impair lipid clearance and promote vascular inflammation. By suppressing nuclear factor kappa B (NF-κB) signaling and enhancing anti-inflammatory cytokine production, vitamin D contributes to a more favorable inflammatory milieu that supports lipid homeostasis and vascular health (Grant et al. 2025).

In populations with a high prevalence of VDD, such as those in the MENA region, these metabolic implications are particularly relevant. Cultural practices limiting sun exposure, low dietary intake of vitamin D-rich foods, and limited access to

supplementation contribute to widespread hypovitaminosis D. In such contexts, correcting vitamin D deficiency may serve as a low-cost, scalable intervention to improve lipid profiles and reduce cardiovascular risk (Hassan et al. 2025).

2.12 RANDOMIZED CONTROLLED TRIALS

2.12.1 Glycaemic Outcomes

Randomized controlled trials of vitamin D supplementation in individuals with prediabetes and type 2 diabetes mellitus have reported mixed glycaemic outcomes. Several studies demonstrated modest improvements in fasting plasma glucose (FPG) and β-cell function (HOMA-B), reflecting enhanced insulin sensitivity. However, effects on HbA1c and 2h postprandial glucose (2hPPBG) were inconsistent, with many trials reporting no significant change (Młynarska et al. 2025). These findings suggest that vitamin D may exert its greatest influence on early insulin dynamics rather than long-term glycaemic control.

2.12.2 Inflammatory Outcomes

RCTs consistently highlight vitamin D's immunomodulatory potential. Supplementation reduced circulating pro-inflammatory cytokines such as IL-6 and TNF-α, while lowering hs CRP levels, thereby attenuating chronic low-grade inflammation. At the same time, anti-inflammatory mediators, including IL-10, were upregulated, supporting immune homeostasis (Ao et al. 2021; Martens et al. 2020). These outcomes underscore vitamin D's role in mitigating the inflammatory milieu that drives insulin resistance and β-cell stress.

2.12.3 Vascular Outcomes

Evidence from RCTs also demonstrates the vascular benefits of vitamin D supplementation. Improvements in endothelial function, measured by flow-mediated dilation (FMD), have been consistently observed in deficient populations. Enhanced nitric oxide bioavailability and reduced arterial stiffness further support vitamin D's

protective role in vascular health (Kim et al. 2020; Surdu et al. 2021). These vascular outcomes highlight vitamin D as a potential adjunct in reducing cardiometabolic risk and slowing atherosclerosis progression.

2.13 META-ANALYSIS AND UMBRELLA REVIEWS

Meta-analyses and umbrella reviews provide pooled evidence supporting the superiority of daily dosing. Roghayeh et al synthesized more than 30 RCTs involving approximately 5,000 participants and reported modest but significant improvements in fasting plasma glucose (average reduction of 5.2 mg/dL) and HOMA-IR (average reduction of 0.8 units). The greatest benefits were observed among individuals with severe baseline deficiency and lower BMI, underscoring the importance of stratified intervention approaches. These findings confirm that vitamin D supplementation is most effective when targeted to populations at the highest risk (Molani-Gol, Rafraf, Asghari Jafarabadi, et al. 2025).

The greatest benefits are consistently seen in individuals with severe baseline deficiency (<20 ng/mL). These subgroups show more pronounced improvements in FPG, HbA1c, and HOMA-IR compared to vitamin D-sufficient participants, highlighting the importance of stratified intervention approaches (Molani-Gol, Rafraf & Safari 2025). This evidence supports targeted supplementation in populations with a high prevalence of deficiency, such as those in the MENA region.

Despite overall positive pooled effects, heterogeneity across trials remains substantial. Differences in dosage regimens (daily vs. intermittent), baseline vitamin D status, ethnicity, BMI, and study design contribute to variability in outcomes. Some meta-analyses report inconsistent effects on HbA1c and 2hPP, reflecting the influence of these moderating factors (Bruna-Mejías et al. 2025).

Dose-response analyses clarify optimal supplementation strategies. Moderate daily doses (3,000–4,000 IU/day) are associated with the most consistent improvements in HbA1c and insulin sensitivity, while higher doses up to 10,000 IU/day remain safe but do not confer additional metabolic benefit (Cao et al. 2025). These findings suggest

that stable, moderate daily dosing is preferable to intermittent bolus regimens, both for efficacy and safety.

2.14 DOSING STRATEGIES AND SAFETY

2.14.1 Daily vs Bolus

Intervention trials have explored a wide range of vitamin D supplementation regimens, including daily low-dose schedules (typically 800–2,000 IU/day, with some studies extending up to 10,000 IU/day) and intermittent high-dose protocols (e.g., 50,000 IU weekly or 60,000 IU monthly). The physiological rationale for daily dosing is that it maintains more stable serum concentrations of [25(OH)D], thereby supporting consistent metabolic and immunomodulatory effects. In contrast, intermittent bolus dosing produces sharp fluctuations in serum levels, which may lead to variable biological responses and less predictable outcomes (Sorrenti et al. 2023).

International guidelines provide structured recommendations for vitamin D dosing. The Endocrine Society's 2024 Clinical Practice Guideline recommends daily supplementation of 600–800 IU for healthy adults, with higher doses (1,500–2,000 IU/day) often required to maintain serum 25(OH)D levels above 30 ng/mL in individuals at risk of deficiency, including those with obesity, darker skin pigmentation, or limited sun exposure (Demay et al. 2024). The guideline also acknowledges that intermittent high-dose regimens (e.g., 50,000 IU weekly or 60,000 IU monthly) can be used in cases of poor adherence, but emphasizes that daily dosing provides more consistent metabolic benefits. Similarly, the European Society of Endocrinology and the World Health Organization (WHO) recommend daily intakes of 600–1,000 IU for adults, with upper safe limits set at 4,000 IU/day for long-term use (Pludowski et al. 2022).

2.14.2 Dose-Response Evidence

Dose-response studies further clarify optimal supplementation strategies. Cao et al demonstrated that reductions in HbA1c were most pronounced at daily doses of 3,000–4,000 IU, while higher doses up to 10,000 IU/day remained safe but did not confer

additional metabolic benefit. This evidence suggests that moderate daily dosing achieves optimal metabolic outcomes without compromising safety, and that escalating doses beyond this threshold may not provide incremental benefit (Cao et al. 2025).

2.14.3 Co-Supplementation

Beyond dosing frequency, co-supplementation strategies have emerged as promising adjuncts. Trials combining vitamin D with magnesium or omega-3 fatty acids revealed synergistic improvements in insulin sensitivity, lipid metabolism, and inflammatory markers compared to vitamin D alone. Chou et al demonstrated that co-supplementation enhanced metabolic outcomes, highlighting the importance of micronutrient interactions in supplementation protocols. These findings suggest that vitamin D should be considered within a broader nutritional framework rather than as a standalone intervention (Chou et al. 2025). Vitamin D and Vitamin K: Synergistic Roles and Emerging Evidence for Combined Supplementation" emphasizes that vitamin D enhances calcium absorption. In contrast, vitamin K2 ensures calcium is directed into bone and prevents vascular calcification. Together, they provide synergistic benefits for bone strength and cardiovascular protection, with emerging evidence showing improved bone mineral density and reduced arterial stiffness compared to vitamin D alone (Khandelwal et al., 2025).

2.14.4 Safety Considerations

Safety profiles across trials remain favorable. Supplementation up to 10,000 IU/day has been consistently reported as safe under biochemical monitoring, with rare adverse events (Cao et al. 2025). Nevertheless, long-term safety data are limited, emphasizing the need for biomarker-guided dosing strategies and stratified interventions tailored to baseline deficiency, body mass index, and regional nutritional contexts.

2.15 GLYCAEMIC BIOMARKERS

FPG, OGTT, and HbA1c remain the cornerstone measures for classifying glycaemic status, with FPG reflecting basal glucose levels after fasting, OGTT assessing glucose

tolerance following a standardized oral load, and HbA1c representing average glycaemia over the preceding two to three months. Additional indices such as FSI, HOMA-IR, and HOMA-B provide deeper insights into insulin dynamics and β-cell responsiveness, with FSI indicating basal insulin secretion, HOMA-IR estimating insulin resistance, and HOMA-B quantifying β-cell function (American Diabetes 2025). Evidence from interventional studies suggests that vitamin D supplementation may modestly reduce FPG and HbA1c, while its effects on insulin indices appear contingent upon baseline vitamin D status, ethnicity, and duration of intervention (Farahmand et al. 2023; Mazahery et al. 2015; Probosari et al. 2025).

2.16 INFLAMMATORY BIOMARKERS

Inflammatory biomarkers such as IL-6, TNF-α, and hs-CRP are central mediators of chronic low-grade inflammation, a key driver of insulin resistance and metabolic syndrome. IL-6 is a pleiotropic cytokine that promotes hepatic glucose output and contributes to systemic insulin resistance. TNF-α impairs insulin signaling pathways by inhibiting insulin receptor substrate activity, thereby exacerbating metabolic dysfunction. hs-CRP, an acute-phase protein produced in the liver under cytokine stimulation, serves as a sensitive marker of systemic inflammation and is consistently elevated in prediabetes and T2DM. Together, these biomarkers reflect the pro-inflammatory milieu that underlies cardiometabolic risk, and their modulation, such as through vitamin D's suppression of NF-κB activation, promotion of Treg differentiation, and reduction of pro-inflammatory cytokines, has been associated with improved metabolic profiles (Cai et al. 2025; Mendes et al. 2020).

2.17 CARDIOVASCULAR BIOMARKERS

Endothelial markers such as FMD, VCAM-1, and E-selectin assess vascular risk. VDD is associated with impaired FMD and arterial stiffness, while supplementation improves endothelial function through enhanced nitric oxide bioavailability and reduced oxidative stress (Cimini et al. 2025). Lipid profiles also correlate with vitamin D status; supplementation often reduces triglycerides and LDL while modestly increasing HDL, though the effects depend on baseline VDD and genetic predisposition (Jafari T 2016).

2.18 HEPATIC, RENAL, AND HEMATOLOGIC BIOMARKERS

ALT, AST, and GGT are established biomarkers of hepatic inflammation and steatosis. Elevated levels of these enzymes indicate hepatocellular injury and metabolic stress, particularly in NAFLD and related disorders. Vitamin D exerts hepatoprotective effects through activation of VDR in hepatocytes and Kupffer cells, which modulates lipid metabolism, suppresses pro-inflammatory cytokine signaling, and attenuates oxidative stress (Federico Ravaioli 2022). Mechanistically, VDR activation downregulates NF-κB pathways, thereby reducing hepatic inflammation, while also influencing PPAR activity to improve lipid handling (Reda et al. 2023).

Clinical evidence supports these mechanistic insights. A recent systematic review and meta-analysis of RCTs reported that vitamin D supplementation significantly reduced serum ALT and AST levels in patients with chronic liver disease, suggesting improvements in hepatocellular integrity (Martinekova et al. 2025). However, despite these biochemical improvements, long-term outcomes such as fibrosis regression, liver stiffness, or survival remain inconclusive. The same review emphasized that while enzyme normalization occurs, there is insufficient evidence to confirm reversal of fibrosis or sustained improvements in liver architecture (Martinekova et al. 2025). Thus, vitamin D supplementation appears to provide short- to medium-term hepatoprotective benefits, particularly in reducing ALT and AST, but further longitudinal studies are required to establish its role in fibrosis regression and long-term clinical outcomes (Rezaei et al. 2021).

Serum creatinine, eGFR, and urinary albumin excretion are critical for assessing kidney function. Vitamin D demonstrates nephroprotective effects through RAAS inhibition, reduced glomerular inflammation, and preservation of podocyte integrity (Bonetti et al. 2003; Emini Sadiku 2025). These mechanisms contribute to the stabilization of eGFR and the reduction of albuminuria.

Haematological indices, particularly full blood count parameters and red cell distribution width (RDW), serve as indirect markers of systemic inflammation, oxidative stress, and metabolic dysregulation. Elevated RDW has been linked to insulin

resistance, endothelial dysfunction, and increased cardiovascular risk. VDD has been linked to anemia of chronic disease and abnormal RDW values, whereas supplementation may help normalize these indices by alleviating inflammation and supporting erythropoiesis (Tonelli et al. 2008).

2.19 GLOBAL GAPS IN EVIDENCE

Meta-analyses and umbrella reviews consistently highlight substantial heterogeneity across randomized controlled trials of vitamin D supplementation. Variability arises from differences in dosage regimens (daily vs. bolus), baseline vitamin D status, ethnicity, BMI, and study design. These methodological inconsistencies contribute to mixed outcomes, particularly for HbA1c and 2HPP, limiting the generalizability of pooled findings (Afraie et al. 2024).

Underrepresentation of LMICs: A critical gap in the evidence base is the underrepresentation of low and middle-income countries (LMICs). Most RCTs and meta-analyses originate from high-income settings in Europe, North America, and parts of Asia, while regions with the highest prevalence of vitamin D deficiency, including the Middle East, North Africa, and Sub-Saharan Africa, remain poorly studied. This imbalance restricts the applicability of findings to populations facing unique nutritional, sociocultural, and environmental determinants of deficiency (Afraie et al. 2024).

2.20 REGIONAL GAPS IN MENA

Despite the high prevalence of vitamin D deficiency across the Middle East and North Africa, randomized controlled trials remain scarce. Most published data are observational or cross-sectional; only a limited number of robust intervention trials have assessed the effects of supplementation on glycaemic control, inflammation, or vascular function. This lack of RCTs limits causal inference and weakens the evidence base for region-specific recommendations (Bassil et al. 2013).

Existing studies in MENA often rely on basic biochemical measures such as serum 25(OH)D and fasting glucose; more comprehensive biomarker panels including

inflammatory cytokines (IL-6, TNF-α), endothelial function markers (FMD, nitric oxide), and hepatic/renal indices (ALT, AST, creatinine, eGFR) are rarely incorporated. The absence of multidimensional biomarker assessment restricts understanding of vitamin D's systemic effects and hampers the development of integrated public health strategies tailored to regional needs (Chakhtoura et al. 2017).

2.21 YEMEN-SPECIFIC GAP

Although vitamin D deficiency is widely suspected to be common in Yemen, there has been no coordinated multicenter prevalence study to establish its true burden across different regions. The limited evidence available stems from small, single-center studies that fail to capture Yemen's geographic, altitudinal, and cultural diversity. In the absence of comprehensive mapping, the formulation of effective national strategies remains constrained.

Research conducted in Yemen has generally taken the form of either observational surveys or small intervention trials. None has combined population-level screening with randomized controlled supplementation within a single framework. This type of integrated design is essential for connecting prevalence data with causal outcomes, and its absence leaves a major gap in understanding how deficiency translates into metabolic and vascular risk in Yemeni populations.

Most Yemeni studies rely on international definitions of deficiency (e.g., <20 ng/mL), but there is no consensus on thresholds tailored to Yemen's unique environmental and nutritional context. High-altitude areas such as Ibb, where cooler climates and heavier clothing reduce sun exposure, may require different reference ranges compared to coastal or lowland regions. Without locally validated thresholds, prevalence estimates may be inaccurate and intervention strategies less effective.

CHAPTER III

METHODOLOGY

3.1 INTRODUCTION

This chapter outlines the methodological framework for achieving the study's objectives. The research was conducted in two sequential phases: an initial cross-sectional survey to determine the prevalence of prediabetes and VDD in the adult population of Ibb Governorate, Yemen, followed by an RCT to evaluate the effects of vitamin D supplementation on metabolic and vascular outcomes among prediabetic individuals.

3.1 STUDY DESIGN

From July 2024 to May 2025, a multicenter dual-phase study was conducted in the Ibb Governorate, Yemen, comprising a population-based cross-sectional survey followed by a randomized controlled trial (RCT). This design provided both epidemiological evidence on the burden of prediabetes and vitamin D deficiency (VDD) and interventional evidence on the effects of vitamin D supplementation in a high-risk subgroup.

Phase I: Cross-sectional survey: Recruitment was performed using non-probability sampling methods, specifically convenience and snowball techniques, across hospitals, academic institutions, and community venues to ensure broad sociodemographic representation. Of 1,233 individuals screened, 1,045 were eligible and enrolled. The prevalence of prediabetes was estimated with 95% confidence intervals, and vitamin D status was assessed within this subgroup to establish the

epidemiological link between glycaemic status and VDD in the local population Figures 3.1 and 3.2.

Phase II – Randomized Controlled Trial: In the second phase, a double-blind, placebo-controlled randomized trial was conducted to assess the effects of vitamin D supplementation on metabolic, inflammatory, and vascular outcomes among prediabetic adults with confirmed vitamin D deficiency (VDD). A total of 151 eligible participants were randomized in equal proportions to receive either high-dose cholecalciferol or placebo for 16 weeks. Randomization was performed manually using a sealed steel container to ensure allocation concealment. Both participants and investigators were blinded to group assignment, and identical packaging was employed to maintain masking throughout the intervention. Follow-up assessments were scheduled at four-week intervals to monitor outcomes (Figure 3.3).

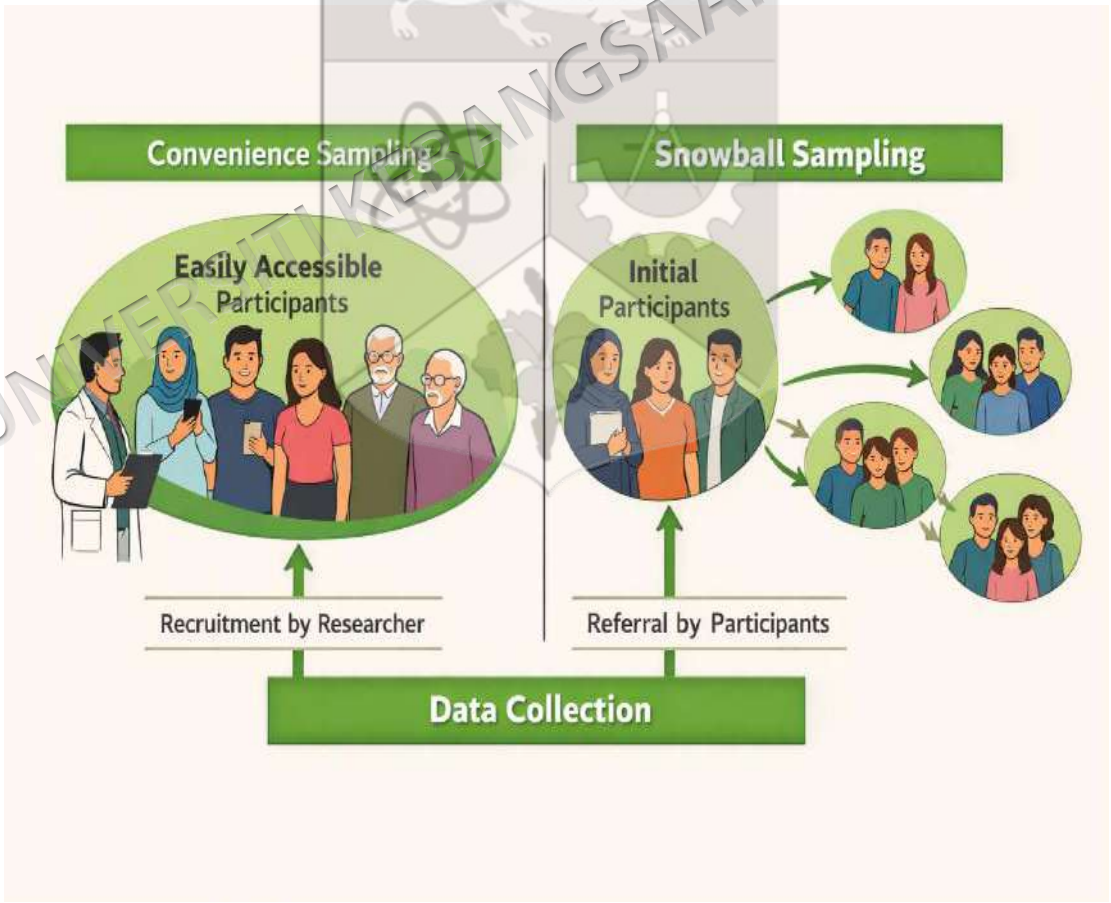

Figure 3.1 Participant Recruitment via Convenience and Snowball Sampling

Figure 3.1. Diagram illustrating participant recruitment through convenience and snowball sampling. The left panel shows researcher-led recruitment of accessible participants, while the right panel depicts participant-driven referrals expanding the sample network. Both approaches contributed to comprehensive data collection across multiple centers in the Ibb Governorate, Yemen.

Figure 3.2 Phase 1: PRE-STUDY DESIGN

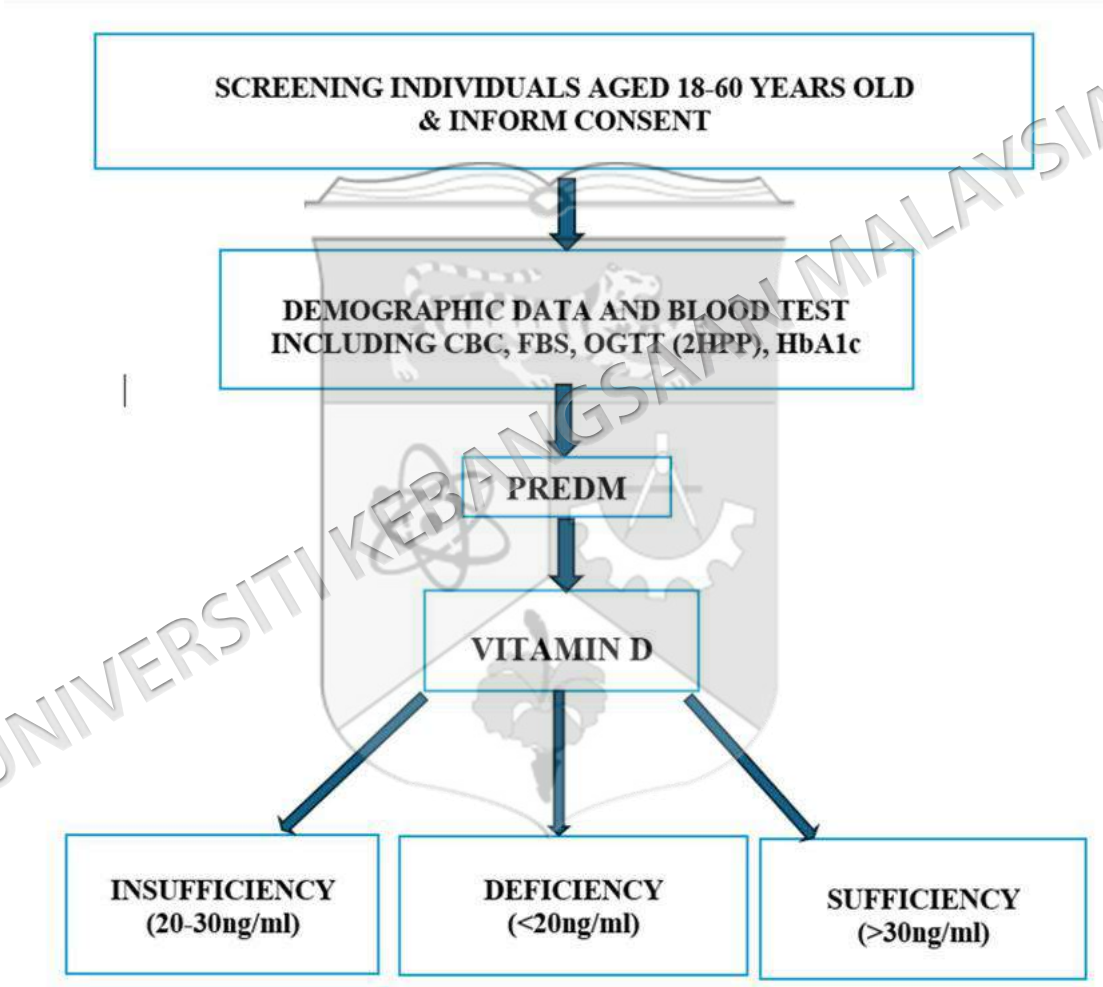

Figure 3.2 Phase I (Cross-sectional survey): Screening and Classification of Prediabetes and Vitamin D status. Schematic representation of the initial study phase, outlining participant screening, eligibility assessment, and baseline data collection before randomization

Figure 3.3. Phase 2 Study

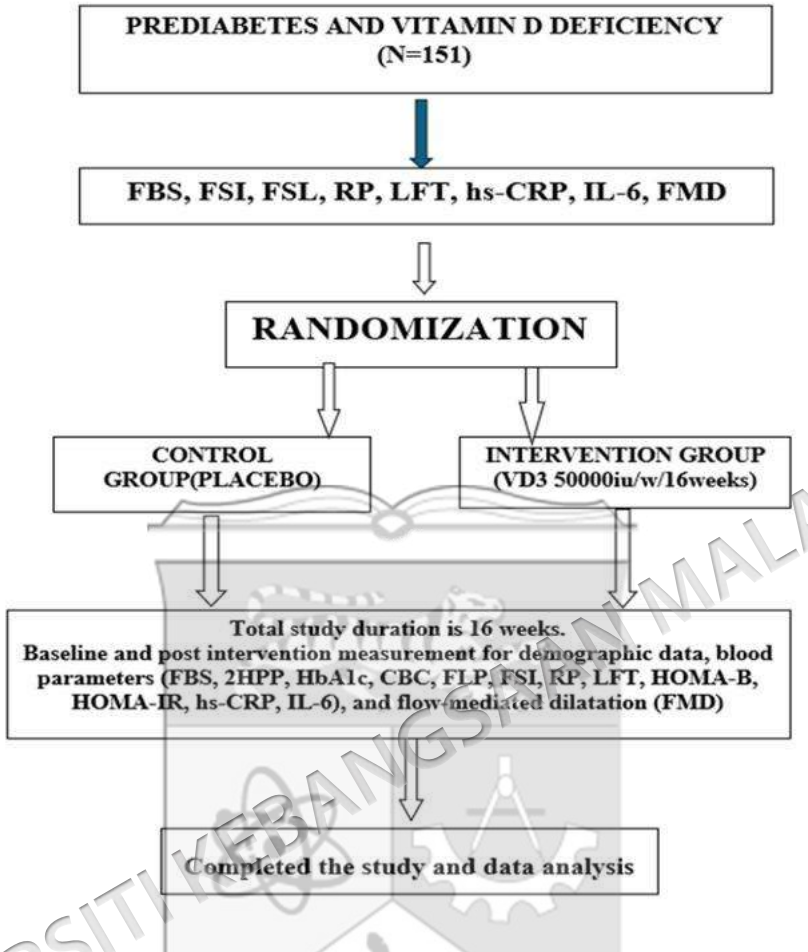

Figure 3.3 Phase II (Randomized Controlled Trial): Study Design and Intervention Flow. Flow diagram illustrating phase II, RCT, including participant allocation to Vitamin D and placebo groups, the intervention, and follow-up assessments

Primary outcomes included changes in fasting blood sugar and serum 25-hydroxyvitamin D concentrations. Secondary outcomes encompassed HbA1c, insulin resistance indices, lipid profile, inflammatory biomarkers, and endothelial function. Outcomes were assessed at baseline and post-intervention, enabling evaluation of both short-term metabolic effects and mechanistic pathways.

3.2 CROSS-SECTIONAL SURVEY

The rationale for conducting a cross-sectional survey before the RCT was firmly grounded in the need to contextualize the intervention within the local metabolic landscape. Comprehensive surveillance data on vitamin D status and prediabetes

prevalence remain unavailable in Yemen, particularly in the Ibb region. This epidemiological gap necessitated a preliminary survey to characterize the target population, refine inclusion criteria, and ensure that the intervention cohort accurately reflected the broader epidemiological profile in the region. Furthermore, the survey facilitated subgroup analyses by gender, urbanicity, and occupational exposure, each of which is a relevant modifier of vitamin D status and glycaemic control. By documenting these variations, the study was able to elucidate the sociocultural and environmental determinants of metabolic health, thereby strengthening the translational relevance of the subsequent interventional phase (Pludowski & Holick, 2022).

3.3.1 Sample Size Calculation

This study was conducted in two phases, each requiring a distinct approach to sample size estimation. The first phase estimated the prevalence of prediabetes in the study population. Using the single-proportion formula with an assumed prevalence of 20% (based on data from neighboring countries such as KSA, UAE, and Oman), a 5% precision, and a 95% confidence level, the required sample size was calculated as 246 participants. This ensured adequate representation for reliable prevalence estimates.

The sample size for estimating the prevalence of prediabetes was calculated using the single proportion formula:

$$n = \frac{Z^2, p\ , (1-p)}{d^2}$$

n = required sample size

Z = standard normal deviate corresponding to the desired confidence level (1.96 for 95%)

p = estimated prevalence

d = margin of error (precision). Assuming a prevalence of 20% (p = 0.20), a precision of 5% (d = 0.05)

95% confidence interval (Arifin 2018).

The minimum required sample size was:

$$n = \frac{(1.96)^2 \cdot 0.20 \cdot 0.80}{(0.05)^2} = 246$$

3.3.2 Eligibility Criteria

Eligibility criteria were carefully defined to ensure both participant safety and methodological rigor. Inclusion criteria encompassed Yemeni adults aged 18 to 60 years. In contrast, exclusion criteria comprised individuals with established diabetes or known prediabetes using antihyperglycemic medications, pregnancy, chronic hepatic or renal disease, personal history of vitamin D supplementation or calcium derivatives for the past 6 months, acute illness at the time of blood sample collection, and morbid obesity defined as BMI greater than or equal to 40 kg/m². These criteria minimized confounding variables and safeguarded the internal validity of both the observational (phase I) and interventional (phase II) phases.

3.3.3 Recruitment Strategy and Site Selection

Recruitment was conducted across multiple urban and semi-urban sites within Ibb, including Jiblah University, Medical City Complex, Al Noor Hospital, and community hubs such as local markets and mosques. This multi-center recruitment strategy was intentionally designed to capture a diverse sample encompassing various occupational, educational, and socioeconomic strata. The inclusion of academic institutions, healthcare facilities, and public marketplaces ensured access to both health-aware individuals and underserved populations, thereby enhancing the external validity and generalizability of the findings.

The selection of Ibb as the principal study site was informed by its distinctive geographic and sociocultural characteristics. Its high-altitude geography and moderate climate, combined with cultural practices that influence sun exposure and dietary patterns, create a unique metabolic environment in which VDD is particularly prevalent. Moreover, Ibb represents a relatively stable zone amidst regional conflict, attracting

populations displaced by civil unrest. These demographic shifts further underscore its relevance as a setting for investigating the interplay between environmental determinants, nutritional status, and metabolic risk. The region's limited access to fortified foods and structured healthcare services highlights the need for locally adapted intervention models, making Ibb an appropriate and strategic choice for this investigation.

3.3.4 Ethical Consideration and Regulatory Compliance

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) standards, ensuring participant rights, dignity, and safety while maintaining scientific integrity. Ethical approval was obtained from the IRBs of Jiblah University for Medical and Health Sciences, Yemen (IRB Ref. JiblahUNI.YEM.772756; Registration No. JiblahUNI.YEM.2025.571), and Universiti Kebangsaan Malaysia (UKM) Research Ethics Committee (Approval No. JEP 2024 680). Confidentiality was safeguarded by anonymizing data, encrypting electronic records, and restricting access to physical documents. Safety monitoring included periodic assessments of serum calcium and renal function, with predefined adverse events tracked. No serious adverse events occurred, and supplementation was well tolerated. Laboratory quality assurance was ensured through standardized protocols, verified reagents, certified facilities, and trained personnel. Interobserver variability was minimized through workshops and standardization sessions. These measures reinforced transparency, participant protection, and methodological rigor, thereby enhancing the study's credibility and translational potential.

3.3.5 Study Population and Sampling

The study population comprised adults aged 18–60 years from Ibb Governorate, Yemen, recruited through hospitals, academic institutions, and community venues, as illustrated in the results.

3.3.6 Biochemical Assessments

Biochemical assessments were conducted to characterize metabolic status, inflammatory profiles, hematological indices, and vascular function at baseline and post-intervention. All participants underwent standardized phlebotomy following an overnight fast of 8–12 hours. Serum and plasma samples were processed within two hours of collection, aliquoted, and stored under controlled conditions until analysis to preserve analyte integrity. Assessments were scheduled at two time points for randomized trial participants: baseline and 16 weeks, whereas cross-sectional participants completed only baseline measurements. Glycaemic indices included FBS, 2HPP, and HbA1c, providing complementary measures of basal glycaemia, postprandial glucose handling, and integrated glycaemic exposure. Fasting serum insulin (FSI) was measured to calculate the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and β-cell function (HOMA-B), thereby quantifying mechanistic aspects of glucose regulation. The lipid profile comprised TC, LDL-C, HDL-C, and TG, offering a comprehensive view of dyslipidemia and cardiometabolic risk.

Hematological parameters were evaluated using FBC, including haemoglobin concentration, red cell distribution width (RDW), and leukocyte counts, which served as indirect markers of systemic inflammation and physiological stress. Liver function tests, renal profile, and urinary albumin (where applicable) were assessed to monitor organ function and detect potential adverse effects. Inflammatory biomarkers included IL-6 and hs-CRP, selected for their established roles in metabolic inflammation and cardiovascular risk stratification.

3.3.7 Endothelial Function Assessment

Endothelial function was evaluated using flow-mediated dilation (FMD) of the brachial artery, performed by a dedicated radiologist with high-resolution ultrasonography in accordance with standardized international protocols. The procedure was conducted by a qualified radiologist, who was responsible for patient preparation, image acquisition, and measurement accuracy. Participants were instructed to rest in a quiet,

temperature-controlled room for at least 10 minutes before the test and to avoid caffeine, smoking, and vigorous exercise for several hours prior.

A sphygmomanometer cuff was placed on the forearm, inflated to occlude blood flow for five minutes, and then released to induce reactive hyperemia. The radiologist measured brachial artery diameter at baseline and again at 60–90 seconds after cuff release, the standard window for peak vasodilation. FMD was calculated as the percentage change in arterial diameter, providing an objective index of endothelial responsiveness.

FMD (%) = (Post-occlusion diameter – Baseline diameter) / Baseline diameter × 100 (Mary C Corretti 1, 2002)

To ensure accuracy, three consecutive measurements were recorded at each time point, and the mean value was used for analysis. All images were stored digitally and reviewed for consistency. Importantly, the dedicated radiologist was blinded to participants' vitamin D status. All measurements were performed consistently by the same radiologist to ensure reproducibility and reduce inter-observer variability.

3.3.8 Laboratory Procedures and Analytical Methods

All laboratory procedures were conducted in certified biomedical facilities under standardized operating protocols to ensure accuracy, reproducibility, and compliance with international quality standards. Samples were processed within two hours of collection, centrifuged to separate serum and plasma, and aliquoted into sterile cryovials. Aliquots were stored at –80°C until analysis to preserve biochemical integrity.

Hematological parameters, including FBC, were measured on the Sysmex XS 500i analyzer (Sysmex Corporation, Japan), which uses fluorescence flow cytometry. Biochemical tests, including glucose, creatinine, liver enzymes (ALT, AST), bilirubin, albumin, cholesterol, triglycerides, HDL, and HbA1c, were analyzed on the Cobas c311 chemistry analyzer (Roche Diagnostics, Germany) using photometric and turbidimetric

methods. Serum 25-hydroxyvitamin D [25(OH)D] concentrations were quantified on the AFIAS 3 Boditech system (Boditech Med Inc., Korea) using a fluorescence immunoassay (FIA). Insulin levels were determined on the ELISA Linear analyzer (Korea) using the sandwich ELISA principle. Interleukin 6 (IL-6) was measured on the iCroma III Boditech platform (Boditech Med Inc., Korea) using fluorescence-based lateral flow immunoassay technology. High-sensitivity C-reactive protein (hs-CRP) was assessed on the Cobas Integra 400 Plus analyzer (Roche Diagnostics, Germany) using turbidimetry.

Quality assurance procedures were rigorously implemented throughout all laboratory processes. Reagents and diagnostic kits were verified for batch integrity, expiration dates, and storage conditions in accordance with manufacturer specifications and international standards. Instruments were calibrated before each analytical run, and duplicate assays were performed on 10% of samples to assess intra-assay variability. Interobserver variability was minimized through pre-study training workshops and standardization sessions. External proficiency testing was also conducted to ensure comparability with international laboratories.

Inflammatory biomarkers, including IL-6 and hs-CRP, were measured using ELISA kits validated for clinical research. Endothelial function was assessed using high-resolution ultrasonography to measure FMD of the brachial artery. Measurements were standardized by conducting assessments in a quiet, temperature-controlled environment, with participants resting supine for at least 10 minutes before evaluation.

Quality assurance procedures included verifying reagent batch integrity, calibrating instruments before each analytical run, and adhering to manufacturer specifications for storage and handling. Duplicate assays were performed on 10% of samples to assess intra-assay variability, and inter-observer variability was minimized through training workshops and standardization sessions conducted before data collection.

3.4 PHASE II: RANDOMISED CONTROLLED TRIAL

3.4.1 Sample Size Calculation

The second phase involved a randomised controlled trial comparing vitamin D supplementation with a placebo among individuals identified as prediabetic. The sample size for this phase was determined using the formula for detecting a difference in means between two independent groups. This calculation incorporated the confidence level, statistical power, variability of the outcome measure, and the minimum clinically significant difference to be detected. With an assumed standard deviation of 20 mg/dL for fasting blood glucose, a minimum detectable difference of 10 mg/dL, a 95% confidence level, and 80% power, the required sample size was 63 participants per group, giving a total of 126 participants. This ensured sufficient statistical power to detect meaningful differences between the intervention and control arms.

For the second phase, which compared two independent groups (vitamin D supplementation versus placebo), the sample size was determined using the formula for detecting a difference in means:

$$n = \frac{2 \cdot (Z_\alpha + Z_\beta)^2 \cdot \sigma^2}{\Delta^2}$$

n = sample size per group

$Z_\alpha/2$ = Z-score for the confidence level (1.96 for 95%)

Z_β = Z-score for the desired power (0.84 for 80%)

σ^2 = variance of the outcome measure = standard deviation

Δ = minimum clinically significant difference

The minimum required sample size was:

$$n = \frac{2 \cdot (1.96 + 0.84)^2 \cdot 20^2}{(10)^2} = 63 \; per \; group$$

Accordingly, the total sample size for Phase 2 was 126 participants (63 per group).

3.4.2 Vitamin D Assessment

Serum 25-hydroxyvitamin D [25(OH)D] was measured as the principal biomarker of vitamin D status. Blood samples were collected after an overnight fast, processed within two hours, and stored at –80°C until analysis. Quantification was performed using a validated enzyme-linked immunosorbent assay (ELISA) kit, standardized against international reference materials. The assay was selected for its sensitivity and specificity in detecting circulating 25(OH)D concentrations, thereby providing an accurate reflection of vitamin D status in the study population.

Internal quality controls were incorporated into each analytical run, including duplicate measurements and calibration against known standards. External proficiency testing was conducted to ensure comparability with international laboratories. Results were expressed in nanograms per milliliter (ng/mL), with deficiency defined as <20 ng/mL, insufficiency as 20–30 ng/mL, and sufficiency as >30 ng/mL, in accordance with widely accepted clinical thresholds.

3.4.3 Additional Biomarkers

In addition to serum 25-hydroxyvitamin D, a comprehensive panel of biochemical and physiological markers was assessed to capture the multidimensional effects of supplementation. Glycaemic indices included FBS, 2HPP, and HbA1c, which together provided measures of basal glycemia, postprandial glucose tolerance, and long-term glycaemic exposure. FSI was quantified to enable calculation of Homeostatic Model Assessment indices for insulin resistance (HOMA-IR) and β-cell function (HOMA-B), thereby providing mechanistic insight into glucose regulation.

The lipid profile reflecting cardiometabolic risk. Inflammatory status was evaluated using hs-CRP and IL-6, both established mediators of metabolic inflammation and vascular dysfunction. Endothelial function was assessed non-

invasively by measuring the brachial artery, performed under standardized conditions using high-resolution ultrasonography.

These biomarkers were selected for their relevance to the pathophysiology of prediabetes and cardiovascular risk, and for their ability to provide mechanistic evidence of vitamin D supplementation's metabolic, vascular, and immunological effects. They complemented the primary vitamin D assessment and strengthened the interpretive framework of the RCT.

3.4.4 Intervention Protocol

Following the identification of eligible participants with concurrent VDD and prediabetic glycaemic profiles, 151 volunteers were enrolled in the RCT. The intervention was designed to rigorously evaluate the efficacy of high-dose vitamin D supplementation in modulating glycaemic control, insulin sensitivity, inflammation, and endothelial function.

3.4.5 Randomization and Blinding

Participants were randomly allocated in a 1:1 ratio into two parallel groups using a simple manual randomization procedure. Allocation was conducted by responsible personnel who discreetly labeled boxes, thoroughly mixed them in a sealed steel container, and recorded assignments to ensure fairness. The process was performed independently of recruitment and outcome assessment, thereby maintaining allocation concealment and minimizing selection bias.

Blinding was maintained across all levels of study personnel, including participants, clinicians, laboratory technicians, and data analysts. Placebo capsules were identical in appearance, taste, and packaging to the active supplement, preserving methodological integrity and reducing performance and detection bias.

3.4.6 Intervention Regimen

During the randomized controlled trial phase, participants were assigned to receive either vitamin D_3 (cholecalciferol) or a matching placebo. The active treatment consisted of oral cholecalciferol capsules (each containing 50,000 IU), administered once weekly for 16 weeks.

A designated pharmacist oversaw dispensing and accountability procedures to ensure methodological rigor. The regimen was selected in line with established therapeutic protocols for correcting vitamin D deficiency, while also balancing efficacy, safety, and participant adherence.

3.4.7 Baseline and Follow-Up Assessments

At baseline, all participants underwent comprehensive clinical and biochemical evaluation, including FBS, 2HPP, HbA1c, FSI, HOMA IR, HOMA-B, lipid profile, liver and renal function tests, FBC, inflammatory markers (IL-6, hs-CRP), and endothelial function assessed by FMD. These assessments were repeated after 16 weeks to enable direct comparison of pre- and post-intervention values.

3.5 COMPLIANCE AND ADHERENCE MONITORING

Participants were systematically monitored throughout the 16-week intervention to ensure adherence to the investigational medicinal product (IMP) and uphold methodological rigor. Follow-up assessments were conducted at four-week intervals, during which capsule counts were performed. At each visit, vital signs, anthropometric measurements, and blood samples were obtained to track progress and safeguard participant safety. Because capsule intake did not occur on the same day for all participants, inter-observer WhatsApp groups were established to provide ongoing reminders and support. These groups functioned as communication platforms through which participants received regular messages reinforcing adherence and were encouraged to document their capsule consumption. Capsule counts at follow-up visits were cross-checked against self-reported intake logs and WhatsApp confirmations to ensure accuracy.

Adherence was defined as consumption of at least 80% of the prescribed capsules during the intervention period. Participants who met or exceeded this threshold were considered compliant and included in the per-protocol analysis, while those below the threshold were flagged for sensitivity analyses.

3.6 SAFETY MONITORING

Safety monitoring was embedded throughout the trial. Participants underwent periodic assessments for serum calcium, renal function, and adverse symptoms. Hypercalcemia, nephrolithiasis, and gastrointestinal disturbances were predefined as adverse events of interest. No serious adverse events were reported, and the supplementation regimen was well tolerated across both arms. Participants were provided with direct contact information for study physicians and encouraged to seek medical attention if needed.

3.7 DATA INTEGRITY AND QUALITY ASSURANCE

All biochemical assays were conducted in certified laboratories using validated methods. Data entry was double-checked by independent personnel, and the trial was registered with a regional clinical trial registry. Standardized operating manuals were employed to ensure reproducibility, transparency, and compliance with international research standards.

The intervention protocol was meticulously designed to evaluate the therapeutic potential of vitamin D_3 supplementation in a high-risk prediabetic population within Yemen. By combining scientific rigor with contextual sensitivity, the protocol leveraged robust blinding procedures, culturally adapted adherence strategies, and comprehensive safety monitoring. This framework supports both internal validity and external applicability, offering a scalable model for micronutrient interventions in resource-constrained settings.

3.8 OUTCOME MEASURES

Outcome measures were defined to evaluate both the primary and secondary objectives of the study, thereby ensuring a comprehensive assessment of the metabolic, vascular,

and inflammatory effects of vitamin D supplementation in prediabetic adults with confirmed vitamin D deficiency.

3.8.1 Primary Outcome

The primary outcome was the change in FBS from baseline to 16 weeks, selected as the most direct and clinically relevant indicator of glycaemic control in prediabetes.

3.8.2 Secondary Outcome

Secondary outcomes encompassed a broad range of biochemical and physiological parameters. Glycaemic indices included 2HPP and HbA1c, which provided complementary measures of postprandial tolerance and long-term glycaemic exposure. Insulin resistance and β-cell function were assessed using FSI, HOMA-IR, and HOMA-B indices, thereby providing mechanistic insight into glucose regulation.

Cardiometabolic risk was evaluated through lipid profile parameters. Inflammatory status was assessed using hs-CRP and IL-6, both established mediators of metabolic inflammation and vascular dysfunction. Endothelial function was measured non-invasively by FMD of the brachial artery, which serves as a surrogate marker of nitric oxide–mediated vascular responsiveness.

3.9 STATISTICAL ANALYSIS

3.9.1 General Statistical Procedures

All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were first examined for distributional characteristics using the Shapiro–Wilk test, which was selected for its superior sensitivity in mild to moderate sample sizes. Visual inspection through histograms and Q–Q plots was employed to complement the statistical tests, thereby ensuring that classification decisions were based on both quantitative and graphical evidence. Variables that satisfied normality assumptions were summarized as

mean and standard deviation, whereas those that deviated from normality were expressed as median and interquartile range. Categorical variables were described as frequencies and percentages.

For normally distributed continuous variables, parametric tests such as the independent-samples t-test, paired-samples t-test, and one-way analysis of variance (ANOVA) were used. When data violated normality assumptions, nonparametric alternatives, including the Mann–Whitney U test, Wilcoxon signed-rank test, and Friedman test, were employed to provide robust inference while accommodating skewed distributions. Associations between categorical variables were examined using the chi-square test of independence, with Fisher's exact test applied in instances where expected cell frequencies fell below five.

Correlation analyses were conducted to explore relationships between serum 25-hydroxyvitamin D concentrations and key metabolic parameters. Pearson's correlation coefficient was used for variables that met parametric assumptions, while Spearman's rank correlation was employed for non-normal variables to capture monotonic associations without assuming linearity. To adjust for potential confounders such as age, sex, and body mass index, multivariable regression models were used, and logistic regression was applied for dichotomous outcomes, such as achieving normoglycemia.

To complement p-values and enhance interpretive depth, effect sizes were calculated for all major comparisons. Cohen's d was reported for t-tests, eta squared for ANOVA, and correlation coefficients for non-parametric analyses. 95% confidence intervals were consistently provided to convey the precision and reliability of point estimates. A p-value of < 0.05 was set as statistical significance.

3.9.2 Randomized Controlled Trial Phase Analyses

In the randomized controlled trial, statistical analyses were designed to evaluate both within-group changes and between-group differences in metabolic, inflammatory, and vascular outcomes, thereby strengthening causal inference. Paired-samples *t*-tests and Wilcoxon signed-rank tests were applied for within-group comparisons, while

independent-samples *t*-tests and Mann–Whitney U tests assessed between-group differences, according to distributional properties. Longitudinal outcomes were analyzed using repeated-measures ANOVA for parametric data and the Friedman test for non-parametric data, enabling assessment of time effects and group × time interactions. Effect sizes (Cohen's *d*, eta squared, and correlation coefficients) and 95% confidence intervals were consistently reported to quantify magnitude and precision. This framework ensured methodological rigor, minimized bias, and enhanced both statistical and clinical interpretability of treatment effects.

3.9.3 Multivariable and Regression Analyses

To account for potential confounders such as age, sex, and body mass index, multivariable regression analyses were performed. Linear regression models were applied to identify independent predictors of post-intervention outcomes, while binary logistic regression was used for dichotomous endpoints, such as achieving normoglycemia. These models enhanced interpretive depth by isolating the independent contribution of vitamin D supplementation while controlling covariates.

3.9.4 Handling Missing Data and Sensitivity Analyses

Missing data were handled using pairwise deletion, allowing the inclusion of all available observations without resorting to listwise deletion. Sensitivity analyses were conducted to evaluate the robustness of findings under different assumptions regarding the mechanism of missingness, including missing completely at random (MCAR) and missing at random (MAR). This approach minimized bias and reinforced the reproducibility of results.

3.9.5 Integration and Methodological Integrity

This structured analysis plan ensured that statistical tests were appropriately matched to the data's distributional properties, that confounding factors were adequately controlled, and that both clinical and statistical relevance were captured through the combined use of p-values, effect sizes, and confidence intervals. By integrating cross-

sectional and interventional analyses within a unified framework, the plan reinforced internal validity, reproducibility, and translational potential of the study outcomes.

3.9.6 Distributional classification of variables

A critical prerequisite for valid statistical inference is the accurate classification of variables according to their distributional properties. This step ensured that the analytical strategy was appropriately aligned with the underlying data structure, thereby enhancing robustness, interpretability, and reproducibility of findings. In biomedical and clinical research, continuous variables often exhibit heterogeneity due to biological variation, environmental influences, and measurement error; hence, careful assessment of normality was indispensable.

Normality was primarily evaluated using the Shapiro–Wilk test, selected for its superior sensitivity in small- to moderate-sample sizes compared with alternative tests such as the Kolmogorov–Smirnov test. Complementary visual diagnostic techniques, including histograms, boxplots, and quantile–quantile (Q–Q) plots, were employed to provide intuitive insights into the shape, symmetry, and tail behaviour of each distribution. Descriptive metrics such as skewness and kurtosis were also calculated to quantify asymmetry and peakedness, while percentile spreads were used to evaluate distributional balance. This triangulated approach ensured that classification decisions were not based on a single diagnostic but rather on a convergence of evidence, thereby minimizing misclassification bias.

3.9.7 Variables Consistent with Normality

Several variables demonstrated distributional characteristics consistent with normality, thereby justifying the use of parametric statistical methods. Age showed near-identical mean and median values, minimal skewness, and slightly negative kurtosis, indicating a symmetric, mildly platykurtic distribution. BMI similarly showed close alignment between the mean and median, very low skewness, and a balanced percentile distribution. Serum creatinine, despite slightly elevated skewness, maintained a narrow and symmetric percentile range, supporting parametric analysis. Low-density

lipoprotein cholesterol displayed acceptable skewness and moderate kurtosis, with evenly spaced percentiles, suggesting a distribution within normal bounds. FMD, although spanning a wide absolute range, exhibited low skewness and negative kurtosis, indicating a bell-shaped distribution. Hemoglobin demonstrated mild skewness and kurtosis with symmetric percentiles, validating parametric testing. Total cholesterol, though slightly skewed, remained within acceptable limits. HbA1c exhibited higher skewness and kurtosis, but its tight interquartile range and sample size justified parametric analysis under the Central Limit Theorem, supporting the robustness of parametric methods in moderately large samples even with mild deviations.

3.9.8 Variables Deviating from Normality

Variables not normally distributed necessitate the use of non-parametric tests, including FBS, 2HPP/OGTT, Serum [25(OH)D], IL-6, Insulin levels, HOMA IR, HOMA B, TG, and HDL cholesterol.

3.9.9 Intention-to-Treat and Per-Protocol Analysis

Two complementary analytical strategies are widely employed in randomised controlled trials:

1. Intention-to-Treat (ITT): ITT analysis includes all participants as originally randomized, regardless of adherence, protocol deviations, or withdrawal. This approach preserves randomization, minimizes bias, and provides an estimate of intervention effectiveness under real-world conditions.

2. Per-Protocol (PP): PP analysis, in contrast, is restricted to participants who fully adhered to the intervention protocol and completed all scheduled assessments. In this study, adherence was operationally defined as consumption of at least 80% of the investigational medicinal product (IMP). This strategy provides insight into the efficacy of an intervention under optimal compliance, though it may introduce bias by excluding non-adherent participants.

CHAPTER IV

RESULTS

4.1 PHASE 1: CROSS-SECTIONAL STUDY (N = 1,045)

4.1.1 Participant Flow and Baseline Characteristics

A total of 1,233 adult participants were initially collected from three medical centers in Ibb Governorate, Yemen. After applying the eligibility criteria, 188 individuals were excluded (Most of the reasons were age> 60 Years, prior DM, and personal history of Vitamin D supplementation or calcium derivatives over the past six months), resulting in 1,045 participants screened for glycaemic status, comprising 617 women (59.0%) and 428 men (41.0%). The mean age of participants was 37.97 ± 11.77 years, and the population was predominantly young adults. There were 354 participants (33.9%) aged 18–30 years, 283 (27.1%) aged 31–40 years, 235 (22.5%) aged 41–50 years, and 173 (16.6%) aged 51–60 years.

The total number of participants with body mass index (BMI) was 355, 132 participants (37.18%) were obese (≥30 kg/m²), 80 (22.53%) were overweight (25–29.9 kg/m²), 128 (36.06%) had normal BMI (18.5–24.9 kg/m²), and 15 (4.23%) were underweight (<18.5 kg/m²). In total, 59.7% of the participants were either in the overweight or obese categories.

The majority of participants (983; 94.1%) reported no family history of chronic disease. Diabetes mellitus was reported in only 28 participants (2.7%), followed by hypothyroidism in 14 (1.3%), hypertension in 13 (1.2%), and a combination of diabetes and hypertension in 4 (0.4%). Cardiac disease was reported exclusively among 3 male participants (0.3%).Table 4.1).

Table 4.1 Demographic and Clinical Characteristics of Participants

Parameter	Total, N (%)	Male, N (%)	Female, N (%)
Total Participants	1045	428 (40.95)	617 (59.05)
Age (years)	37.97 ± 11.77 *	—	—
Age Group			
18–30 years	354 (33.9)	97 (22.7)	257 (41.7)
31–40 years	283 (27.1)	126 (29.4)	157 (25.4)
41–50 years	235 (22.5)	110 (25.7)	125 (20.3)
51–60 years	173 (16.6)	95 (22.2)	78 (12.6)
Family History of Chronic Disease			
None	983 (94.1)	394 (92.1)	589 (95.5)
Diabetes Mellitus	28 (2.7)	19 (4.4)	9 (1.5)
Hypothyroidism	14 (1.3)	5 (1.2)	9 (1.5)
Hypertension	13 (1.2)	9 (2.1)	4 (0.6)
Hypertension & Diabetes	4 (0.4)	1 (0.2)	3 (0.5)
Cardiac Disease	3 (0.3)	3 (0.7)	0 (0.0)

Legend: All values are expressed as frequencies (N) with percentages (%) except age* is presented as mean ± SD

4.1.2 Prevalence of Prediabetes

The evaluation of glycaemic status revealed a considerable prevalence of prediabetes across diagnostic modalities. Based on FBS, 245 participants (23.4%) were classified as prediabetic, comprising 113 males (46.1%) and 132 females (53.9%). Using the 2HPP test, 154 participants (14.7%) were identified as prediabetic, including 72 males (46.8%) and 82 females (53.2%). The HbA1c criterion yielded the highest prevalence: 276 participants (26.4%) were classified as prediabetic, comprising 123 males (44.6%) and 153 females (55.4%), Table 4.2.

Table 4.2 Glycaemic Status Distribution by Diagnostic Test (n = 1045)

Diagnostic Test	Normal N (%)	Prediabetes N (%)	Diabetes N (%)	Total N
FBS	654 (62.6)	245 (23.4)	146 (14.0)	1045
OGTT	786 (75.2)	154 (14.7)	105 (10.0)	1045
HbA1c	589 (56.4)	276 (26.4)	180 (17.2)	1045

Legend: Glycaemic status was classified using ADA criteria (FBS, OGTT, HbA1c).

4.1.3 Prevalence of Vitamin D Deficiency

Of the 276 participants classified as prediabetic based on HbA1c levels, only 266 underwent vitamin D evaluation. Of these, 197 (74.1%) had vitamin D deficiency (<20 ng/mL), 51 (19.2%) had insufficiency (20–30 ng/mL), and 18 (6.8%) had sufficient levels (>30 ng/mL). Among those with a deficiency, 110 were female (55.8%), and 87 were male (44.2%). Vitamin D insufficiency was more common in males (n = 29; 56.9%) than in females (n = 22; 43.1%). However, equal numbers of cases were observed for sufficient vitamin D levels among males and females (9 males, 9 females), Table 4.3.

Table 4.3 Vitamin D Status in HbA1c-defined prediabetics (n = 266)

Category	Total N (%)	Male N (%)	Female N (%)
Deficient (<20 ng/mL)	197 (74.1)	87 (44.2)	110 (55.8)
Insufficient (20–29 ng/mL)	51 (19.2)	29 (56.9)	22 (43.1)
Sufficient (≥30 ng/mL)	18 (6.8)	9 (50.0)	9 (50.0)

Legend: All values are expressed as frequency and percentages. More than 70% of prediabetic participants had vitamin D deficiency and were predominantly female.

4.1.4 Undiagnosed T2DM

The prevalence of undiagnosed diabetes mellitus was evaluated using integrated diagnostic criteria, revealing significant differences in detection rates across test pairings. The highest number of cases was identified when FBS was combined with HbA1c or when OGTT was paired with HbA1c, with each combination detecting 102 cases (9.76% of the cohort). The FBS + OGTT combination, on the other hand, found 88 cases (8.42%).

Across all diagnostic combinations, females consistently represented a higher proportion of undiagnosed cases. For example, using the FBS + HbA1c criteria identified 59 women (5.64%) compared with 43 men (4.11%), and a similar female predominance was observed with the OGTT + HbA1c combination. (Table 4.2 and Table 4.).

Table 4.4 Prevalence of Undiagnosed Diabetes by Combined Diagnostic Criteria in the Study Population (n = 1045)

Diagnostic Test Pair	Total Diabetes Cases N (%)	Female N (%)	Male N (%)
FBS + OGTT	88 (8.42)	51 (4.88)	37 (3.54)
FBS + HbA1c	102 (9.76)	59 (5.64)	43 (4.11)
OGTT + HbA1c	102 (9.76)	59 (5.64)	43 (4.11)

Legend: All values are expressed as percentages (%).

4.1.5 Analysis of Demographic Variables Demonstrated Clear Associations with Glycaemic Indices

Analysis of demographic and clinical variables demonstrated clear associations with glycaemic indices. Age group was strongly associated with glycaemic status across all diagnostic measures: FBS ($\chi^2 = 141.27$, $p < 0.001$), OGTT ($\chi^2 = 184.25$, $p < 0.001$), and HbA1c ($\chi^2 = 251.90$, $p < 0.001$)—with prevalence of prediabetes and diabetes rising progressively with advancing age. Gender also showed significant associations with FBS ($\chi^2 = 10.50$, $p = 0.005$) and HbA1c ($\chi^2 = 15.18$, $p = 0.001$), where males were more frequently classified as normal and females more often fell into the represented abnormal categories; however, no significant association was observed with OGTT ($\chi^2 = 2.92$, $p = 0.232$). Family history of diabetes was only significantly associated with HbA1c ($\chi^2 = 21.11$, $p = 0.020$), suggesting its influence on long-term glycaemic control rather than short-term indices. Vitamin D deficiency (VDD) was not significantly correlated with FBS or OGTT; however, a weak positive correlation was detected with HbA1c ($\rho = 0.200$, $p = 0.014$), suggesting a possible association between VDD and long-term glycaemic dysregulation Table 4.5.

Table 4.5 Association Between Participant Characteristics (Factors) and Glycaemic Status by Diagnostic Test (n=1045)

Variable Pair	Test	Chi-square (χ^2, df)	p-value
Age Group × Glycaemic Status	FBS	141.27 (df = 6)	**<0.001**
	OGTT	184.25 (df = 6)	**<0.001**
	HbA1c	251.90 (df = 6)	**<0.001**

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Gender × Glycaemic Status	FBS	10.50 (df = 2)	**0.005**
	OGTT	2.92 (df = 2)	0.232
	HbA1c	15.18 (df = 2)	**0.001**
Family History × Glycaemic Status	FBS	6.95 (df = 10)	0.730
	OGTT	8.45 (df = 10)	0.585
	HbA1c	21.11 (df = 10)	**0.020***
VDD × Glycemic status	FBS	0.117	**0.154**
	OGTT	0.115	**0.159**
	HbA1c	0.200	**0.014**

Legend: Significant associations ($p < 0.05$) are observed.

4.2 PHASE 2: RANDOMIZED CONTROLLED TRIAL (N = 151)

4.2.1 Baseline Characteristics

Of the total 1045 participants from phase 1, 197 who met the criteria were eligible for the phase 2 randomized controlled trial. A total of 151 eligible volunteers (who agreed to participate in phase 2 and provided signed informed consent) were uniformly classified as prediabetic according to the American Diabetes Association (ADA) criteria. In addition, every participant demonstrated vitamin D deficiency, defined as serum 25(OH)D concentrations below 20 ng/mL.

Baseline assessment encompassed demographic, anthropometric, metabolic, vascular, inflammatory, and lipid parameters. Statistical comparison of these variables revealed no significant differences between the Vitamin D and placebo groups, thereby confirming the comparability of the two arms at study outset. The baseline characteristics are presented in two subsections: the overall demographic and clinical profile of the entire cohort, and the group-wise comparison between Vitamin D and placebo participants (**Table 4.**).

Table 4.6 Baseline Demographic and Clinical Characteristics of Study Participants, prediabetes with vitamin D deficiency (Pre Intervention, n = 151)

Variable	Category	N (%)
Gender	Female	81 (53.6)
	Male	70 (46.4)
Age categories	18–30 yrs	24 (15.9)
	31–40 yrs	60 (39.7)
	41–50 yrs	46 (30.5)
	51–60 yrs	21 (13.9)
BMI categories	Normal (18.5–24.9)	35 (23.2)
	Overweight (25–29.9)	59 (39.1)
	Obese (≥30)	57 (37.7)
FBS categories	Normal (<100 mg/dL)	64 (42.4)
	Prediabetes (100–125 mg/dL)	82 (54.3)
	Diabetes (>125 mg/dL)	5 (3.3)
OGTT categories	Normal (<140 mg/dL)	117 (77.5)
	IGT (140–199 mg/dL)	34 (22.5)
HbA1c categories	Normal (<5.7%)	4 (2.6)
	Prediabetes (5.7–6.4%)	147 (97.4)
	Diabetes (≥6.5%)	0 (0)
HOMA-IR categories	Optimal (<1.5)	23 (15.2)
	Early IR (1.5–1.9)	20 (13.2)
	Moderate IR (2–2.9)	55 (36.4)
	Significant IR (≥3)	53 (35.1)
HOMA-B categories	Hyperfunction (>120)	62 (41.1)
	Optimal (70–120)	52 (34.4)
	Reduced (<70)	37 (24.5)
FMD categories	Normal (>6.5%)	84 (55.6)
	Borderline (3.1–6.4%)	19 (12.6)
	Dysfunction (<3.1%)	48 (31.8)
IL-6 categories	Normal (<10 pg/mL)	79 (52.3)
	Mild (10–15.9 pg/mL)	46 (30.5)
	Moderate (16–50 pg/mL)	19 (12.6)
	Severe (>50 pg/mL)	7 (4.6)
hs-CRP categories	Low (<1 mg/L)	105 (69.5)
	Moderate (1–3 mg/L)	12 (7.9)
	High (>3 mg/L)	34 (22.5)
Lipid profile	Total Cholesterol ≥200	65 (43.0)
	Triglycerides ≥150	101 (66.9)
	HDL <40	75 (49.7)
	LDL ≥100	98 (64.9)

Legend: All variables are reported as frequencies (N) and percentages (%). The study cohort demonstrated a substantial prevalence of overweight and obesity, accompanied by insulin resistance, lipid abnormalities, and elevated inflammatory markers

The demographic and clinical profile of the study population reflects a uniform baseline status. All participants met ADA criteria for prediabetes and exhibited vitamin D deficiency, ensuring homogeneity across the cohort. The study population comprised 151 adults, with a near-equal sex distribution of 53.6% females and 46.4% males, and an age range spanning 18 to 60 years. This uniform classification established a consistent metabolic and nutritional foundation for the trial, providing a reliable basis for subsequent randomization and group-wise comparisons.

The mean BMI of the study population was 28.58 ± 4.19 kg/m². The median vitamin D level was 11.02 (7.30-13.50). Median glycemic parameters, including FBS, 2HPP, and HbA1c, were 100.00 (95.00-105.00), 129.00 (121.00-139.00), and 5.8 (5.70-6.00), respectively. Median fasting serum insulin was 10.69 (7.59 – 14.44) with HOMA-B of 107.54 (70.54-147.17) and 2.54 (1.94-3.62) HOMA-IR. Assessment of vascular function using FMD was 7.14% (2.44-13.1). Inflammatory markers, including IL-6, was 4.28 (1.00-11.52) pg/mL, and hs-CRP was 0.55 (0.35-1.24) mg/L. Mean total CHO and LDL were 197.97 ± 42.61 mg/dL and 118.23 ± 34.94 mg/dL, respectively. Triglyceride levels were 180.00 mg/dL (132.00–257.00), while HDL concentrations measured 40.00 mg/dL (35.00–42.00)

4.2.2 Pre-intervention Association Between Vitamin D Deficiency Levels and Glycaemic, Insulin Resistance, and Inflammatory Markers

Vitamin D levels showed a significant positive correlation with HbA1c ($\rho = 0.200$, $p = 0.014$) and a significant inverse correlation with hs-CRP ($\rho = –0.237$, $p = 0.003$). However, no significant correlations were observed with FBS, 2hPPBG, HOMA-IR, HOMA-B, or IL-6. Vitamin D showed a significant association with hs-CRP ($\chi^2 = 7.103$, $p = 0.029$), confirming that lower vitamin D status was linked to higher inflammatory risk. But no associations were observed with glycemic or insulin resistance groups. Hence, these findings indicate that vitamin D is most consistently

associated with systemic inflammation (hs-CRP), while its relationship with glycemia is evident only with HbA1c, and no robust link was found with insulin resistance (Table 4.7).

Table 4.7 Association of Vitamin D Status with Glycaemic, Inflammatory, and Insulin Resistance Indices (Pre-intervention)

Outcome Variable	Spearman's rho	p (Spearman)	χ^2 (df)	p (Chi-square)
FBS	–0.133	0.104	10.267 (4)	0.036
2hPPBG	0.070	0.391	7.252 (4)	0.123
HbA1c	0.144	0.078	1.974 (4)	0.741
HOMA-IR	–0.157	0.054	1.169 (6)	0.978
HOMA-B	–0.026	0.748	4.894 (4)	0.298
hs-CRP	–0.090	0.271	6.044 (4)	0.196
IL-6	–0.220	0.007	10.136 (6)	0.119 (linear-by-linear p = 0.005)

Legend: *Spearman's correlation (rho) and Chi-square (χ^2) tests were used to assess post-intervention associations between vitamin D status and glycaemic, inflammatory, and insulin resistance indices. Significant associations were observed for fasting blood sugar (χ^2, p = 0.036) and IL-6 (rho, p = 0.007; linear-by-linear p = 0.005). Other indices showed no statistically significant relationships (p > 0.05).*

4.2.3 Baseline Comparison Between The Vitamin D and Placebo Groups

A comprehensive comparison of baseline demographic, anthropometric, metabolic, vascular, inflammatory, and lipid parameters was undertaken between the Vitamin D and placebo groups before intervention. The mean BMI was 28.81 ± 6.96 kg/m² in the Vitamin D group and 28.89 ± 5.96 kg/m² in the placebo group (p = 0.629). Both groups demonstrated comparable body composition, with overweight and obesity being the predominant categories. FBS was 100.0 [95.0–106.0] mg/dL in the Vitamin D group and 100.0 [95.0–105.0] mg/dL in the placebo group (p = 0.381). The OGTT was 128.5 [118.0–140.0] mg/dL versus 129.0 [121.0–139.0] mg/dL (p = 0.128). HbA1c was identical in both groups, 5.80 [5.65–5.95] % (p = 0.730). These findings confirm that glycemic control was similar across groups at baseline, with values consistent with ADA-defined prediabetes.

Serum 25(OH)D was 11.03 [7.0–14.3] ng/mL in the Vitamin D group and 11.02 [7.0–13.2] ng/mL in the placebo group (p = 0.933). This demonstrates uniform VDD across both arms, with no baseline difference. HOMA B was 110.37 [65.0–175.0] in the Vitamin D group and 107.54 [70.0–184.0] in the placebo group (p = 0.953). HOMA IR was 2.78 [2.0–4.0] versus 2.54 [1.5–4.2] (p = 0.317). These results indicate comparable degrees of insulin resistance and β-cell function between groups at baseline.

FMD was 7.42 [3.0–17.0] % in the Vitamin D group and 7.14 [3.0–14.0] % in the placebo group (p = 0.154). This shows that endothelial function was similar across groups, with no significant difference before intervention. IL-6 was 3.54 [2.0–12.0] pg/mL in the Vitamin D group and 4.28 [2.0–13.0] pg/mL in the placebo group (p = 0.237). hs CRP was 0.46 [0.2–1.1] mg/L versus 0.55 [0.3–1.2] mg/L (p = 0.181). Total CHOL was 197.49 ± 40.16 mg/dL in the Vitamin D group and 198.47 ± 38.49 mg/dL in the placebo group (p = 0.997). TG were 188.5 [133.0–265.0] mg/dL versus 180.0 [127.0–228.0] mg/dL (p = 0.310). HDL was 39.5 [34.0–42.0] mg/dL versus 40.0 [35.0–42.0] mg/dL (p = 0.399). LDL was 118.13 ± 40.75 mg/dL versus 118.33 ± 52.00 mg/dL (p = 0.941). The absence of significant differences (all p-values > 0.05) suggests robust group homogeneity and effective randomization.**Table 4.**).

Table 4.8 Baseline Comparison of Clinical and Biochemical Parameters Between Vitamin D and Placebo

Parameter	**Vitamin D Group (n = 76) Median (IQR)**	**Placebo Group (n = 75) Median (IQR)**	**p value**
BMI (kg/m²)	28.81 ± 6.96*	28.89 ± 5.96*	0.629
FBS (mg/dL)	100.0 [95.0–106.0]	100.0 [95.0–105.0]	0.381
2HPP (mg/dL)	128.5 [118.0–140.0]	129.0 [121.0–139.0]	0.128
HbA1c (%)	5.80 [5.65–5.95]	5.80 [5.65–5.95]	0.730
25(OH)D (ng/mL)	11.03 [7.0–14.3]	11.02 [7.0–13.2]	0.933
HOMA-B	**107.54 (70.54–147.17)**	**103.39 (67.50–177.41)**	0.953
HOMA-IR	**2.54 (1.94–3.61)**	**2.22 (1.76–3.85)**	**0.294**
FMD (%)	7.42 [3.0–17.0]	7.14 [3.0–14.0]	0.154
IL-6 (pg/mL)	3.54 [2.0–12.0]	4.28 [2.0–13.0]	0.237
hs-CRP (mg/L)	0.46 [0.2–1.1]	0.55 [0.3–1.2]	0.181
Total Chol (mg/dL)	197.49 ± 40.16*	198.47 ± 38.49*	0.997
TG (mg/dL)	188.5 [133.0–265.0]	180.0 [127.0–228.0]	0.310
HDL (mg/dL)	39.5 [34.0–42.0]	40.0 [35.0–42.0]	0.399
LDL (mg/dL)	118.13 ± 40.75*	118.33 ± 52.00*	0.941

Legend: Data are presented as median (IQR), except for variables marked with *, which are expressed as mean ± SD. Between-group comparisons were performed using the Mann–Whitney test, except for * where the Student's t-test was applied. A p-value < 0.05 was considered statistically significant

4.2.4 Post-Intervention Outcomes in Prediabetic Adults Receiving Vitamin D or Placebo

4.2.4.1 Vitamin D group (76)

There were 76 adults in the Vitamin D group, with a slight majority of women (n = 45, 59.2%) compared to men (n = 31, 40.8%). Table 8 shows the age distribution, which indicates that most people were in the middle-aged group. In particular, 19 participants (25.0%) were 18 to 30 years old, 30 (39.5%) were 31 to 40 years old, 22 (28.9%) were 41 to 50 years old, and 6 (7.9%) were 51 to 60 years old.

Anthropometric assessment revealed that 38.2% (n = 29) were overweight, 36.8% (n = 28) obese, and 25.0% (n = 19) normal weight. Baseline vitamin D status confirmed universal deficiency (<20 ng/mL) in all participants (100%; n = 76).

Metabolic indices demonstrated that 30 participants (39.5%) had normal fasting glucose, 43 (56.6%) were prediabetic, and 3 (3.9%) were diabetic. OGTT was normal in 62 participants (81.6%) and impaired in 14 (18.4%), with no cases of diabetes detected. HbA1c distribution showed 2 participants (2.6%) within the normal range and 74 (97.4%) classified as prediabetic.

HOMA IR indicated optimal insulin sensitivity in 10 participants (13.2%), while 61 (80.2%) had varying degrees of insulin resistance: 5 (6.6%) early IR, 34 (44.7%) moderate IR, and 27 (35.5%) significant IR. HOMA B showed compensatory hyperfunction (>120) in 30 participants (39.5%), optimal function in 30 (39.5%), and reduced function in 16 (21.1%).

Inflammatory markers showed elevated IL-6 in nearly half of participants, with 45 (59.2%) within the optimal range (<10 pg/mL). Mild elevation was seen in 19 (25.0%), moderate in 9 (11.8%), and severe in 3 (3.9%). hs CRP showed 17 participants

(22.4%) at high risk (>3.1 mg/L), 5 (6.6%) at moderate risk (1–3 mg/L), and 54 (71.1%) at low risk (<1 mg/L).

Lipid abnormalities were common: 51 participants (67.1%) had elevated triglycerides, 38 (50.0%) had low HDL, and 50 (65.8%) had elevated LDL. Endothelial function was impaired in 26 participants (34.2%), borderline in 9 (11.8%), and normal in 41 (53.9%).

4.2.4.2 Placebo Group (n = 75)

The placebo group comprised 75 adults, with a slight male predominance (52.0%, n = 39) compared to females (48.0%, n = 36). The age distribution is illustrated in Table 8, showing that most participants were concentrated in the middle-aged categories: 12 individuals (16.0%) were aged 18–30 years, 26 (34.7%) were aged 31–40 years, 22 (29.3%) were aged 41–50 years, and 15 (20.0%) were aged 51–60 years.

Glycaemic classification based on the fasting blood glucose was normal in 34 participants (45.3%), prediabetic in 39 (52.0%), and diabetic in 2 (2.7%). OGTT was normal in 55 participants (73.3%) and impaired in 20 (26.7%). HbA1c distribution revealed 2 participants (2.7%) within the normal range and 73 (97.3%) classified as prediabetic. Vitamin D deficiency was universal (100%).

Insulin resistance was widespread: HOMA IR was optimal in 13 participants (17.3%), early IR in 15 (20.0%), moderate IR in 21 (28.0%), and significant IR in 26 (34.7%). β-cell function (HOMA B) showed hyperfunction in 32 participants (42.7%), optimal in 22 (29.3%), and reduced in 21 (28.0%). Endothelial function (FMD) was normal in 43 participants (57.3%), borderline in 10 (13.3%), and dysfunctional in 22 (29.3%).

Inflammatory markers revealed IL-6 normal in 34 participants (45.3%), mild elevation in 27 (36.0%), moderate in 10 (13.3%), and severe in 4 (5.3%). hs CRP was low in 51 participants (68.0%), moderate in 7 (9.3%), and high in 17 (22.7%). Lipid abnormalities were common: 50 participants (66.7%) had elevated triglycerides, 38 (50.7%) had low HDL, and 48 (64.0%) had elevated LDL (Table 4.9).

Table 4.9 Metabolic, Vascular, and Inflammatory Outcomes in Prediabetic Adults Receiving Vitamin D or Placebo (Baseline vs. Post-Intervention)

Variable	Category	Vitamin D pre (n=76) N (%)	Vitamin D Group Post N (%)	Placebo pre (n=75) N (%)	Placebo Group Post N (%)
FBS	Normal	30 (39.5)	63 (82.9)	34 (45.3)	31 (41.3)
	Prediabetes	43 (56.6)	13 (17.1)	39 (52.0)	39 (52.0)
	Diabetes	3 (3.9)	0 (0)	2 (2.7)	5 (6.7)
OGTT (2hPPBG)	Normal	62 (81.6)	70 (92.1)	55 (73.3)	68 (90.7)
	Prediabetes	14 (18.4)	5 (6.6)	20 (26.7)	7 (9.3)
	Diabetes	0 (0)	1 (1.3)	–	–
HbA1c	Normal	2 (2.6)	48 (63.2)	2 (2.7)	43 (57.3)
	Prediabetes	74 (97.4)	25 (32.9)	73 (97.3)	28 (37.3)
	Diabetes	0 (0)	3 (3.9)	0 (0)	4 (5.3)
Vitamin D Status	Deficiency (<20 ng/mL)	76 (100)	18 (23.7)	75 (100)	74 (98.7)
	Insufficiency (20–30 ng/mL)	0 (0)	18 (23.7)	0 (0)	1 (1.3)
	Sufficiency (>30 ng/mL)	0 (0)	40 (52.6)	–	–
HOMA-IR	Optimal (<1.5)	10 (13.2)	29 (38.2)	13 (17.3)	24 (32.0)
	Early IR (1.5–1.9)	5 (6.6)	17 (22.4)	15 (20.0)	15 (20.0)
	Moderate IR (2–2.9)	34 (44.7)	15 (19.7)	21 (28.0)	21 (28.0)
	Significant IR (≥3.0)	27 (35.5)	15 (19.7)	26 (34.7)	15 (20.0)
HOMA-B	Hyperfunction (>120)	30 (39.5)	28 (36.8)	32 (42.7)	16 (21.3)
	Optimal (70–120)	30 (39.5)	26 (34.2)	22 (29.3)	23 (30.7)
	Reduced (<70)	16 (21.1)	22 (28. 9)	21 (28.0)	36 (48.0)

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FMD	Normal (>6.4)	41 (53.9)	61 (80.3)	43 (57.3)	27 (36.0)
	Borderline (3.1–6.4)	9 (11.8)	4 (5.3)	10 (13.3)	9 (12.0)
	Dysfunction (<3.1)	26 (34.2)	11 (14.5)	22 (29.3)	39 (52.0)
IL-6	Normal (<10)	45 (59.2)	39 (51.3)	34 (45.3)	30 (40.0)
	Mild (10–15.9)	19 (25.0)	13 (17.1)	27 (36.0)	15 (20.0)
	Moderate (16–50)	9 (11.8)	17 (22.4)	10 (13.3)	18 (24.0)
	Severe (>50)	3 (3.9)	7 (9.2)	4 (5.3)	12 (16.0)
hs-CRP	Low (<1)	54 (71.1)	12 (15.8)	51 (68.0)	19 (25.3)
	Moderate (1–3.1)	5 (6.6)	44 (57.9)	7 (9.3)	28 (37.3)
	High (>3.1)	17 (22.4)	20 (26.3)	17 (22.7)	28 (37.3)
Lipids	T. Chol <200	44 (57.9)	54 (71.1)	42 (56.0)	49 (65.3)
	≥200	32 (42.1)	22(28.9)	33 (44.0%)	26 (34.7%)
	TG <150	25 (32.9)	38 (50.0)	25 (33.3)	32 (42.7)
	TG ≥150	51 (67.1)	38(50.0)	50 (66.7%)	43 (57.3%)
	HDL<40	38 (50.0)	38 (50.0%)	37 (49.3%)	34 (45.3%)
	HDL≥40	38 (50.0)	38 (50.0)	38 (50.7)	41 (54.7)
	LDL <100	26 (34.2%)	16 (21.3)	27 (36.0)	16 (21.3)
	LDL=100–129	23 (30.3%)	30 (39.5%)	23 (30.7%)	26 (34.7%)
	LDL ≥130	27 (35.5)	30 (39.5%)	25 (33.3%)	33 (44.0%)

Legend: Values are shown as frequency (N) and percentage (%). Categories follow ADA and standard clinical cut-offs for glycaemia, insulin resistance (HOMA-IR), β-cell function (HOMA-B), endothelial function (FMD), inflammatory markers (IL-6, hs-CRP), and lipid profile.

4.2.5 Post-Intervention Changes in the Vitamin D Group (N = 76)

Following 16 weeks of vitamin D supplementation, several metabolic, inflammatory, and cardiovascular parameters were reassessed to determine post-intervention changes. BMI decreased significantly from 28.81 ± 6.96 kg/m² to 27.59 ± 6.30 kg/m² (p = 0.009), reflecting modest weight reduction.

While FBS reduced from 100.00 mg/dL (95.00–105.50) to 94.00 mg/dL (88.00–100.00), p < 0.001. Similar findings with 2HPP, decreased from 128.50 mg/dL (118.00–139.25) to 113.00 mg/dL (100.00–126.00), p < 0.001. HbA1c also showed improvement from 5.80% (5.65–5.95) to 5.60% (5.40–5.80), p < 0.001. These findings confirm significant improvement in glycaemic control.

Insulin resistance, as reflected by HOMA-IR, declined significantly from 2.78 (2.00–4.00) to 1.72 (1.00–3.10), with p < 0.001. In contrast, HOMA-B showed a modest reduction from 110.37 (64.70–175.07) to 94.79 (65.00–173.00), which was not statistically significant (p = 0.580). Vitamin D level (25(OH)D) rose markedly from 11.03 ng/mL (7.30–14.33) to 31.13 ng/mL (22.00–41.01), p < 0.001, demonstrating effective correction of deficiency. FMD improved significantly from 7.42% (3.00–17.00) to 15.47% (9.00–24.00), p < 0.001, reflecting enhanced endothelial function. Inflammatory markers showed IL-6 increased from 3.54 pg/mL (2.00–12.29) to 9.49 pg/mL (5.00–25.00), p = 0.009. hs CRP rose from 0.46 mg/L (0.20–1.11) to 2.01 mg/L (1.00–3.00), p = 0.020.

Total cholesterol decreased significantly from 197.49 ± 40.16 mg/dL to 177.54 ± 33.63 mg/dL (p < 0.001). A comparable reduction was observed in triglycerides, declining from 188.50 mg/dL (132.25–264.75) to 152.00 mg/dL (93.50–206.75) (p < 0.001). LDL rose slightly from 118.13 ± 34.18 mg/dL to

125.00 ± 36.49 mg/dL, but this change did not reach statistical significance (p = 0.113). In contrast, HDL remained at a median of 39.50 mg/dL, shifting from 34.00–42.00 to 34.00–46.00, and this improvement achieved statistical significance (p = 0.049), as shown in Table 4.10.

Table 4.10 Baseline and Post-Intervention Metabolic, Vascular, and Inflammatory Parameters in Prediabetic Adults (Vitamin D vs. Placebo)

Parameter	Vitamin D Group (n=76) Baseline Median (IQR)	Vitamin D Group Post Median (IQR)	p-value	Placebo Group (n=75) Baseline Median (IQR)	Placebo Group Post Median (IQR)	p-value
BMI (kg/m²)	28.43 ± 4.35*	27.65 ± 4.28*	0.009	28.72 ± 3.91*	27.59 ± 3.79*	< .001
FBS (mg/dL)	100.0 [95–106]	94.0 [88–100]	< .001	100.0 [95–105]	100.0 [90–111]	0.106
2HPP (mg/dL)	128.5 [118–139]	113.0 [100–126]	< .001	130.0 [121–139]	115.0 [100–131]	< .001
HbA1c (%)	5.80 [5.65–5.95]	5.60 [5.40–5.80]	< .001	5.80 [5.65–5.95]	5.50 [5.25–5.75]	< .001
25(OH)D (ng/mL)	11.03 [7.0–14.3]	31.13 [22.0–41.1]	< .001	10.80 [7.0–13.1]	10.64 [7.0–13.95]	0.747
HOMA-B	110.37 [65–175]	94.79 [65–173]	0.580	103.39 [65–175]	72.16 [50–121]	< .001
HOMA-IR	2.78 (2.14–3.42)	1.72 (1.20–2.60)	< .001	2.22 [1.5–3.8]	1.97 [1.2–3.0]	< .001
FMD (%)	7.42 [3.0–17.0]	15.47 [9.0–24.0]	< .001	6.90 [3.0–18.0]	2.70 [1.0–11.0]	< .001
IL-6 (pg/mL)	3.54 [2.0–12.0]	9.49 [5.0–25.0]	0.009	5.68 [3.0–15.0]	13.25 [7.0–34.0]	< .001
hs-CRP (mg/L)	0.46 [0.2–1.1]	2.01 [1.0–3.0]	0.020	0.60 [0.3–1.2]	2.05 [1.0–5.0]	< .001
Total Chol (mg/dL)	197.49 ± 40.16*	177.54 ± 33.63*	< .001	198.47 ± 45.23*	187.39 ± 38.49*	0.025
Triglycerides (mg/dL)	188.5 [133–265]	152.0 [93.5–206.8]	< .001	179.0 [128–229]	158.0 [110–210]	0.262
HDL (mg/dL)	39.5 [34–42]	39.5 [34–46]	0.049	40.0 [35–42]	40.0 [34–48]	0.076
LDL (mg/dL)	118.13 ± 34.18*	125.01 ± 36.49*	0.113	118.33 ± 35.91*	129.52 ± 41.85*	0.042

Legend: Values are median (IQR) or mean ± SD (*). p-values show within-group changes

4.2.6 Post-Intervention Changes in the Placebo Group (N = 75)

After 16 weeks without supplementation, fasting blood glucose categories worsened slightly, with diabetes prevalence rising from 2 (2.7%) to 5 (6.7%). OGTT improved numerically, with 68 participants (90.7%) normal and only 7 (9.3%) impaired. HbA1c showed apparent normalization in 43 participants (57.3%), but 4 (5.3%) progressed to diabetes.

Vitamin D deficiency persisted almost universally (74/75, 98.7%), with only one case of insufficiency. Endothelial function deteriorated, with normal FMD declining from 43 (57.3%) to 27 (36.0%), and dysfunction rising from 22 (29.3%) to 39 (52.0%).

Inflammatory markers worsened: IL-6 moderate/severe elevations increased from 14 participants (18.6%) to 30 (40.0%), and hs CRP high-risk cases increased from 17 (22.7%) to 28 (37.3%). Lipid profiles showed modest improvements in total cholesterol and HDL, but LDL worsened, with normal cases declining from 27 (36.0%) to 16 (21.3%). While β-cell reserve declined, rising from 21 (28.0%) to 36 (48.0%). (Table 14).

β-cell reserve declined, with reduced function rising from 21 (28.0%) to 36 (48.0%). BMI decreased significantly from 28.72 ± 3.91 to 27.59 ± 3.79 kg/m² ($p < 0.001$). FBS showed no significant change ($p = 0.106$), but 2HPP improved from 130.0 [121.0–139.0] to 115.0 [100.0–131.0] mg/dL ($p < 0.001$). HbA1c decreased significantly from 5.80 [5.65–5.95] to 5.50 [5.25–5.75] % ($p < 0.001$).

Vitamin D levels remained unchanged ($p = 0.747$). HOMA B declined significantly from 103.39 [65.0–175.0] to 72.16 [50.0–121.0] ($p < 0.001$), while HOMA IR improved modestly from 2.22 [1.5–3.8] to 1.97 [1.2–3.0] ($p < 0.001$). Endothelial function worsened, with FMD decreasing from 6.90 [3.0–18.0] % to 2.70 [1.0–11.0] % ($p < 0.001$). Inflammation increased, with IL-6 rising from 5.68 [3.0–15.0] to 13.25 [7.0–34.0] pg/mL ($p < 0.001$) and hs CRP from 0.60 [0.3–1.2] to 2.05 [1.0–5.0] mg/L ($p < 0.001$).

Lipid changes included a reduction in total cholesterol (198.47 ± 45.23 to 187.39 ± 38.49 mg/dL, p = 0.025), no significant change in triglycerides (p = 0.262) or HDL (p = 0.076), and a significant increase in LDL (118.33 ± 35.91 to 129.52 ± 41.85 mg/dL, p = 0.042) (**Error! Reference source not found.**).

4.2.7 Post-Intervention Comparison Between Vitamin D and Placebo

Following 16 weeks of intervention, categorical and continuous outcomes were compared between the Vitamin D group (n = 76) and the placebo group (n = 75). For FBS, 63 participants (82.9%) in the Vitamin D group achieved normal values, 13 (17.1%) remained prediabetic, and none progressed to diabetes. In the placebo group, 31 participants (41.3%) achieved normal values, 39 (52.0%) remained prediabetic, and 5 (6.7%) progressed to diabetes ($\chi^2 = 18.74$, $p < 0.001$). Median FBS was 94.0 mg/dL [88.0–100.0] in the Vitamin D group compared to 101.0 mg/dL [94.0–108.0] in the placebo group ($p < 0.001$).

OGTT was normal in 70 participants (92.1%) in the Vitamin D group and 68 (90.7%) in the placebo group. Prediabetes was observed in 5 (6.6%) and 7 (9.3%), respectively, with one diabetic case (1.3%) in the Vitamin D group and none in the placebo group (p = 0.599). Median 2HPP was 113.0 mg/dL [100.0–126.0] versus 115.0 mg/dL [102.0–128.0] (p = 0.690). HbA1c normalization occurred in 48 participants (63.2%) in the Vitamin D group and 43 (57.3%) in the placebo group. Prediabetes persisted in 25 (32.9%) and 28 (37.3%) individuals, while diabetes was present in 3 (3.9%) and 4 (5.3%) individuals, respectively ($\chi^2 = 6.12$, $p = 0.047$). Median HbA1c was identical at 5.60% [5.4–5.8] in both groups (p = 0.979).

Vitamin D status showed marked divergence. In the Vitamin D group, 40 participants (52.6%) achieved sufficiency (>30 ng/mL), 18 (23.7%) reached insufficiency (20–30 ng/mL), and 18 (23.7%) remained deficient (<20 ng/mL). In the placebo group, deficiency persisted in 74 participants (98.7%), and only 1 participant (1.3%) had insufficiency. Median serum 25(OH)D was 31.13 ng/mL [22.0–41.1] in the Vitamin D group compared to 10.64 ng/mL [7.00–13.95] in the placebo group ($p < 0.001$).

Insulin sensitivity, measured by HOMA IR, was optimal (<1.5) in 29 participants (38.2%) in the Vitamin D group and 24 (32.0%) in the placebo group. Significant IR (≥3.0) was observed in 15 participants (19.7%) and 15 (20.0%), respectively. Median HOMA IR was 1.72 [1.0–3.1] versus 1.97 [1.1–2.6] (p = 0.306).

β-cell function (HOMA-B) was reduced (<70) in 22 participants (28.9%) in the Vitamin D group compared to 36 (48.0%) in the placebo group. Hyperfunction (>120) was more prevalent in the Vitamin D group (28 participants, 36.8%) than in the placebo group (16 participants, 21.3%). Median HOMA B was 94.79 [65.0–173.0] versus 72.16 [50.0–121.0] (p = 0.028).

Endothelial function, assessed by FMD, was normal (>6.4%) in 61 participants (80.3%) in the Vitamin D group compared to 27 (36.0%) in the placebo group. Dysfunction (<3.1%) was present in 11 participants (14.5%) and 39 (52.0%), respectively. Median FMD was 15.47% [9.0–24.2] versus 8.57% [5.0–15.0] (p < 0.001).

Inflammatory markers showed IL-6 normalization (<10 pg/mL) in 39 participants (51.3%) in the Vitamin D group and 30 (40.0%) in the placebo group, with severe elevations (>50 pg/mL) in 7 (9.2%) and 12 (16.0%), respectively. Median IL 6 was 9.49 pg/mL [5.0–18.0] versus 11.86 pg/mL [6.0–28.0] (p = 0.080). hs CRP was low (<1 mg/L) in 12 participants (15.8%) in the Vitamin D group and 19 (25.3%) in the placebo group, with high risk (>3.1 mg/L) in 20 (26.3%) and 28 (37.3%), respectively. Median hs CRP was 2.01 mg/L [1.0–4.0] in both groups (p = 0.468).

Anthropometric and lipid parameters were comparable. Mean BMI was 27.65 ± 4.28 in the Vitamin D group and 27.59 ± 3.79 in the placebo group (p = 0.935). Total cholesterol was 177.54 ± 33.63 mg/dL versus 187.39 ± 38.49 mg/dL (p = 0.142). Triglycerides were normal (<150 mg/dL) in 38 participants (50.0%) in the Vitamin D group and 32 (42.7%) in the placebo group, with median values of 163.24 [93.50–206.75] versus 180.07 [110.00–210.00] (p = 0.445). HDL ≥40 mg/dL was observed in 38 participants (50.0%) in the Vitamin D group and 41 (54.7%) in the placebo group,

with median values of 39.5 [34.00–46.00] versus 40.0 [34.0–48.0] (p = 0.677). LDL <100 mg/dL was present in 16 participants (21.1%) in both groups, with mean values of 125.01 ± 36.49 versus 129.52 ± 41.85 (p = 0.395), Table 4.10.

CHAPTER V

DISCUSSION

5.1 OVERVIEW OF FINDINGS

In the cross-sectional phase, prediabetes prevalence in Ibb was high: HbA1c identified 26.4%, fasting glucose 23.4%, and 2-hour postprandial 14.7%, placing Yemen at the upper end of regional estimates (15–30%). HbA1c proved the most sensitive and pragmatic tool in resource-limited settings, given its stability and independence from acute intake (Selvin et al., 2010; Sherwani et al., 2016; ADA, 2024). Importantly, female participants were disproportionately affected, explained by higher BMI in the overweight–obese range and sociocultural factors such as limited sun exposure leading to vitamin D deficiency, both of which compound insulin resistance and increase prediabetes risk.

Vitamin D deficiency was alarmingly widespread. Within the HbA1c-defined prediabetic subgroup (n = 266), 74.1% were deficient (<20 ng/mL), 19.2% insufficient (20–30 ng/mL), and only 6.7% sufficient (>30 ng/mL). Female predominance was evident, with women comprising 55.8% of deficient cases. This disparity reflects sociocultural practices (veiling, reduced sun exposure, limited outdoor mobility), biological determinants (adiposity, hormonal fluctuations), and lifestyle factors (low physical activity, menopausal transition) (Alshahrani et al., 2013; Palacios, 2014; Holick, 2007). Family history of diabetes also showed a significant association with HbA1c-defined prediabetes, reinforcing its role as a determinant of long-term glucose regulation. Collectively, these findings confirm that prediabetes and vitamin D deficiency coexist at high rates, creating a dual burden of metabolic and micronutrient risk (Seida, 2014; Chakhtoura, 2017; Angelino et al., 2023).

The randomized controlled trial demonstrated clear metabolic and vascular benefits of high-dose vitamin D supplementation (50,000 IU/week for 16 weeks). Fasting glucose decreased significantly in the intervention group (100.0 → 94.0 mg/dL, $p < 0.001$), with a higher proportion achieving normoglycaemia (82.9% vs. 41.3% in placebo). These findings are consistent with prior trials reporting beneficial effects of vitamin D on fasting glucose in prediabetic and insulin-resistant populations (Elsayed et al., 2023; Mirhosseini et al., 2018). HbA1c remained stable in the supplemented group but trended upward in placebo participants, consistent with the short intervention period (Pittas et al., 2019). HOMA-B values were preserved in the vitamin D group (median 94.79 vs. 72.16 in placebo, $p = 0.028$), indicating maintenance of β-cell reserve, while HOMA-IR showed no significant improvement ($p = 0.306$) (Klec et al., 2019; Riachy et al., 2006). Endothelial function improved markedly in the vitamin D group (FMD 7.42% → 15.47%), contrasting with deterioration in placebo participants (6.90% → 2.70%, $p < 0.001$). These changes are clinically meaningful, as impaired FMD predicts cardiovascular events (Tarcin et al., 2009; Yuen-Fung, 2013).

Inflammatory markers (IL-6, hs-CRP) rose in both groups, but increases were less pronounced in the vitamin D arm, suggesting attenuation rather than reversal of systemic inflammation. Severe IL-6 elevations (>50 pg/mL) and high-risk hs-CRP (>3 mg/L) were less frequent in the intervention group, consistent with international evidence that vitamin D modulates but does not abolish inflammatory activation (Mirhosseini et al., 2018; Arabi et al., 2010; Jorde et al., 2010; Schleithoff et al., 2006; Mazidi et al., 2018; Mousa et al., 2016). Lipid parameters showed modest within-group changes, but between-group differences were not statistically significant, reflecting the short trial duration and the context-dependent nature of vitamin D's impact on lipid metabolism (Ge et al., 2025; Lu et al., 2024).

Overall, the placebo group exhibited deterioration across glycaemic, β-cell, vascular, and inflammatory domains, underscoring the natural trajectory of prediabetes in high-risk populations (Steven et al., 2005; Adam, 2012). In contrast, vitamin D supplementation attenuated disease progression, producing significant improvements in fasting glucose, β-cell function, and endothelial responsiveness, while partially modulating inflammation. These findings support vitamin D's role as a pragmatic

adjunct in early metabolic and vascular risk management (Pittas et al., 2019; Barbarawi et al., 2019).

5.2 PHASE 1: EPIDEMIOLOGICAL INSIGHTS

5.2.1 Burden of Prediabetes

Prediabetes constitutes a substantial public health burden in this Yemeni cohort. HbA1c identified 26.4% of participants as prediabetic, fasting blood glucose 23.4%, and 2-hour postprandial glucose 14.7%. These figures place Yemen at the upper end of prevalence estimates reported across the Middle East and North Africa (15–30%), underscoring the country's vulnerability to the global rise in dysglycaemia (Riekki et al., 2025).

The domestic implications are considerable: nearly one-quarter of adults are already at elevated risk of progressing to type 2 diabetes, with attendant complications that could strain Yemen's fragile healthcare infrastructure. Internationally, these findings reinforce the recognition of prediabetes as a growing epidemic in low- and middle-income countries, where early detection and preventive strategies remain limited.

Gender stratification revealed consistently higher rates among women, confirming a disproportionate burden that mirrors regional patterns. This highlights the need for gender-sensitive public health interventions. Collectively, the evidence demonstrates that prediabetes is not only a clinical finding but a pressing epidemiological challenge, both nationally and within the broader MENA context.

5.2.2 Burden of Vitamin D Deficiency

Vitamin D deficiency emerged as an even greater burden than prediabetes in this Yemeni cohort. Within the HbA1c-defined prediabetic subgroup (n = 266), 74.1% were deficient (<20 ng/mL), 19.2% insufficient (20–30 ng/mL), and only 6.7% sufficient (>30 ng/mL). These figures confirm an extremely high prevalence, far exceeding global averages of 20–40% reported in Western populations, and consistent with endemic

hypovitaminosis D documented across the Middle East and North Africa (Bassil et al., 2013; Seida, 2014).

The domestic implications are profound: three-quarters of prediabetic adults are simultaneously vitamin D deficient, compounding their risk of progression to type 2 diabetes and cardiovascular disease. This dual burden places Yemen among the countries most severely affected by overlapping metabolic and nutritional challenges, with serious consequences for its already strained healthcare system.

Female predominance was evident, with women comprising 55.8% of deficient cases. The female predominance observed among participants with prediabetes may be attributed to sociocultural factors such as limited sun exposure due to traditional clothing practices, which contribute to vitamin D deficiency, as well as the higher prevalence of overweight and obesity among women, both of which are strongly linked to impaired glucose metabolism. To enhance clarity and ensure alignment with the study objectives, the discussion was reorganized into thematic subsections: (a) impact on glycemic control, addressing fasting blood glucose, 2-hour postprandial glucose, and HbA1c outcomes; (b) impact on insulin resistance and β-cell function, focusing on HOMA-IR and HOMA-B indices; and (c) impact on inflammatory biomarkers, including IL-6 and hs-CRP. This structure provides a logical progression from glycemic outcomes to mechanistic pathways. The conclusion was also streamlined to emphasize the principal findings, highlighting the beneficial role of vitamin D supplementation in improving glycemic control, insulin resistance, and inflammatory status among adults with prediabetes, while avoiding unnecessary repetition.

This mirrors regional findings where sociocultural practices, including traditional clothing limiting sun exposure, reduced outdoor mobility, and dietary insufficiency, restrict endogenous vitamin D synthesis and intake (Alshahrani et al., 2013). Biological contributors, such as adiposity and hormonal influences, further exacerbate vulnerability (Palacios, 2014; Holick, 2007). In summary, vitamin D deficiency represents a severe epidemiological burden in Yemen, with prevalence rates among the highest reported globally, disproportionately affecting women, and driven by cultural and environmental determinants.

5.2.3 Coexistence of Prediabetes and Vitamin D Deficiency

The analysis revealed a strong coexistence of prediabetes and vitamin D deficiency in this Yemeni cohort, with the majority of prediabetic individuals also deficient in 25(OH)D. While sociocultural determinants such as limited sun exposure remain relevant (Bassil et al., 2013; Seida, 2014), our findings highlight that adiposity is a central contributor. Female prediabetics exhibited BMI values in the overweight–obese range, consistent with evidence that adiposity both reduces vitamin D bioavailability through sequestration in adipose tissue and exacerbates insulin resistance (Pittas et al., 2019; Al-Shahrani et al., 2016; Al-Daghri et al., 2018). Thus, the overlap is not solely attributable to environmental exposure but also to intrinsic metabolic stressors. This underscores the need for integrated strategies targeting both obesity and vitamin D deficiency in high-risk populations.

5.3 PHASE 2: METABOLIC EFFECTS OF VITAMIN D SUPPLEMENTATION

5.3.1 Glycaemic Outcomes

Vitamin D supplementation was associated with a significant reduction in fasting glucose (100.0 → 94.0 mg/dL, $p < 0.001$), whereas glucose levels in the placebo group remained stable. This clinically meaningful reduction mirrors findings in Canadian prediabetic adults, in which supplementation lowered fasting glucose and improved glycaemic control (Mirhosseini et al., 2018).

Postprandial glucose improved in the intervention group but remained unchanged in the placebo group. Similar improvements have been reported in Middle Eastern cohorts (Elsayed et al., 2023), while the U.S. D2d trial found no significant effect on postprandial outcomes, underscoring variability across populations (Pittas et al., 2019).

Changes in HbA1c were modest. The supplemented group showed stabilization, while placebo participants trended upward. This modest effect is consistent with the relatively short intervention period, as HbA1c reflects longer-term glycaemic exposure. Comparable modest changes were noted in the D2d trial (Pittas et al., 2019).

Post-intervention comparison revealed no significant difference in HOMA-IR between the vitamin D and placebo groups ($p = 0.306$). Median values were slightly lower in the vitamin D arm, suggesting a numerical trend toward reduced insulin resistance, but this did not reach statistical significance (Klec et al., 2019).

In addition to the comparative findings with published literature, our results may be explained by several plausible mechanisms through which Vitamin D contributes to the stabilization of β-cell integrity and enhancement of insulin secretion. Vitamin D, via its nuclear receptor (VDR), regulates the transcription of genes involved in insulin synthesis and secretion. It also modulates intracellular calcium flux, which is essential for glucose-stimulated insulin release. Furthermore, Vitamin D exerts anti-inflammatory and antioxidant effects, reducing cytokine-mediated β-cell damage and oxidative stress. By improving peripheral insulin sensitivity, Vitamin D decreases the secretory burden on β-cells, thereby preserving their functional capacity. Collectively, these mechanisms provide a biological rationale for the observed improvements in HOMA-B and related indices in the intervention group.

Overall, vitamin D supplementation improved fasting and postprandial glucose and stabilized HbA1c, while attenuating insulin resistance compared to placebo. These findings align with smaller international trials (Elsayed et al., 2023; Klec et al., 2019; Mirhosseini et al., 2018) but differ from larger multicenter studies (Pittas et al., 2019), highlighting population-specific responses and the importance of baseline deficiency in determining outcomes.

5.3.2 Metabolic–Vascular Model

The dual-phase findings of this investigation support a conceptual model in which vitamin D exerts selective physiological targeting, acting preferentially on pancreatic β-cell preservation and endothelial function, with secondary modulation of glycaemic indices and inflammatory pathways.

Vitamin D supplementation stabilized HOMA-B, suggesting preservation of β-cell reserve, whereas the placebo group showed significant deterioration. This

preservation is clinically relevant, as early impairment of insulin secretion is a hallmark of prediabetes and a predictor of progression to type 2 diabetes. Similar protective effects have been reported in randomized trials among vitamin D-deficient populations (Begum et al., 2023; Probosari et al., 2025; Mitri et al., 2011). Mechanistic studies demonstrate that vitamin D enhances insulin secretion by modulating intracellular calcium flux and upregulating insulin gene transcription (Pittas, 2007; Norman, 1980). VDRs expressed on β-cells reduce cytokine-induced apoptosis and support insulin gene activity (Chiu et al., 2004; Maestro et al., 2000). Meta-analyses further confirm modest but significant improvements in β-cell function and reduced progression to diabetes in deficient populations (Krul-Poel et al., 2014; Bruna Mejías et al., 2025).

The most prominent vascular outcome was the improvement in FMD observed in the vitamin D group (7.4% → 15.5%), contrasted by a decline among placebo participants (6.9% → 2.7%). This divergence highlights vitamin D's potential to restore endothelial function in deficient prediabetic adults. Comparable improvements have been reported in randomized trials (Tarcin, 2009; Dong, 2010) and supported by meta-analytic evidence (Musazadeh et al., 2025). Endothelial dysfunction is an early marker of atherosclerosis and cardiovascular risk (Alexander et al., 2021), and improvements of this magnitude are clinically meaningful, as impaired FMD predicts future cardiovascular events (Heiss et al., 2023). Mechanistically, vitamin D upregulates endothelial nitric oxide synthase (eNOS), increases nitric oxide bioavailability, and reduces oxidative stress, thereby enhancing vasodilation and arterial compliance (Borgi, 2017; Tarcin, 2009; Dong, 2010).

Vitamin D supplementation was associated with significant reductions in fasting blood glucose, indicating improved glycaemic regulation. Notably, HbA1c decreased in both vitamin D and placebo groups, suggesting that the effect may not be attributable solely to vitamin D. These findings are consistent with meta-analyses reporting that supplementation improves glycaemic indices, particularly in individuals with baseline deficiency (Zhang et al., 2021). Despite metabolic and vascular improvements, both groups showed increases in IL-6 and hs-CRP, with less severe increases in the vitamin D arm. This paradox underscores the intricate nature of immunometabolic regulation. Systematic reviews confirm that vitamin D attenuates but does not reverse

inflammatory escalation, with heterogeneous effects across populations (Mazidi et al., 2018; Mousa et al., 2016; Bruna Mejías et al., 2025). Genetic variability in VDR and DBP polymorphisms may further explain differential responses (Uitterlinden et al., 2004).

This integrated model suggests that vitamin D acts preferentially on β-cell function and endothelial health, with secondary modulation of glycaemia and inflammation. Such selective targeting underscores vitamin D's potential as a pragmatic adjunct in prediabetes management, while also highlighting the need for longer interventions to capture its full metabolic and immunological effects.

5.4 INFLAMMATORY OUTCOMES: THE PARADOX

Both arms exhibited significant elevations in circulating inflammatory markers, namely IL-6 and hs-CRP, during the intervention period. The magnitude of increase was comparatively lower in the vitamin D group, indicating partial attenuation of systemic inflammation.

This paradoxical rise has been noted in other randomized trials, where vitamin D supplementation attenuated but did not fully suppress increases in inflammatory markers (Mazidi et al., 2018; Mousa et al., 2016). Meta-analyses confirm that vitamin D's anti-inflammatory effects are context-dependent, with stronger benefits observed in populations with higher baseline inflammation or longer intervention durations (Calton et al., 2015; Gropper, 2023).

Elevated inflammatory markers during colder months are well documented, largely due to increased infection prevalence and reduced sunlight exposure. Winter periods are associated with lower serum 25(OH)D levels and higher systemic inflammation, which may have contributed to the overall rise in IL-6 and hs-CRP observed in both groups (Mendes et al., 2024; Wyse et al., 2020). Similar seasonal influences have been reported in European and Middle Eastern cohorts, where winter deficiency coincided with elevated CRP and cytokine levels (Dopico et al., 2015).

The overlap with Ramadan introduced dietary and behavioral changes that independently modulate inflammatory status. Altered meal timing, increased carbohydrate intake, and prolonged fasting periods have been shown to influence cytokine dynamics and CRP levels. Studies conducted in Middle Eastern cohorts confirm that Ramadan fasting may transiently enhance glycaemic control but also raise inflammatory markers, contingent on diet. Such cultural practices may have amplified biomarker changes in the placebo group, while vitamin D supplementation partially mitigated these effects (Elmajnoun et al., 2023; Jahrami, 2025).

Systemic inflammation in prediabetes is multifactorial, influenced not only by metabolic dysregulation but also by contextual and environmental exposures. Lifestyle factors such as sedentary behavior, poor diet quality, and sleep disruption have been consistently linked to elevated CRP and IL-6 levels (Mendes et al., 2024; Wyse et al., 2020). Environmental triggers, including air pollution and toxin exposure, further amplify cytokine release and oxidative stress (Ao et al., 2021). These influences interact with obesity and visceral adiposity, which are well-established drivers of systemic inflammation through secretion of IL-6, TNF-α, and other adipokines (Ao et al., 2021). Insulin resistance and hyperglycaemia also contribute to oxidative stress and activation of inflammatory cascades, reinforcing the metabolic-inflammatory link in prediabetes (Mazidi et al., 2018; Mousa et al., 2016).

Finally, genetic variability, particularly polymorphisms in the vitamin D receptor (VDR) and vitamin D binding protein (DBP), modulates responsiveness to supplementation and may explain heterogeneous inflammatory responses across populations (Uitterlinden et al., 2004). Mechanistic studies further support vitamin D's role in suppressing NF-κB signaling and reducing cytokine release, but clinical translation remains variable (Yin et al., 2014).

Vitamin D supplementation mitigated the progression of inflammation rather than reversing it. Participants receiving vitamin D exhibited smaller rises in IL-6 and hs-CRP compared with those on placebo, reflecting partial modulation of systemic inflammatory activity. This trajectory aligns with randomized trials demonstrating that vitamin D slows the escalation of inflammatory biomarkers without fully restoring them to normal levels (Mazidi et al., 2018; Mousa et al., 2016).

Such attenuation is clinically relevant: even modest reductions in inflammatory progression may lower long-term cardiometabolic risk, particularly in prediabetic populations where chronic low-grade inflammation accelerates vascular and glycaemic deterioration (Pradhan et al., 2001). Meta-analyses emphasize that vitamin D's immunomodulatory effects are context-dependent, with stronger benefits in individuals with baseline deficiency or prolonged exposure (Calton et al., 2015; Gropper, 2023).

Thus, the paradoxical rise in both groups, coupled with attenuation in the vitamin D arm, suggests that supplementation may act as a stabilizer rather than a suppressor of inflammation in the short term. Longer interventions, higher dosing, or stratification by baseline inflammatory status may be required to achieve reversal rather than attenuation.

5.5 LIPID PROFILE AND CARDIOMETABOLIC RISK

Vitamin D supplementation led to modest within-group reductions in triglycerides and total cholesterol. Although these changes were clinically relevant—given that elevated TG and total cholesterol are independent predictors of cardiometabolic risk—similar reductions in total cholesterol were also observed in the placebo group, and between-group comparisons did not reach statistical significance. This suggests that lipid improvements may not be attributable solely to vitamin D. These findings are consistent with previous randomized controlled trials and meta-analyses, which generally report neutral or modest effects of vitamin D on lipid parameters, particularly in populations with baseline deficiency (Ge et al., 2025; Lu et al., 2024; Mazidi et al., 2018). Mechanistically, vitamin D may reduce hepatic lipogenesis and improve insulin sensitivity, indirectly lowering TG levels (Al-Daghri et al., 2015).

HDL-C remained largely unchanged in both groups. This finding is consistent with the majority of clinical trials, which have failed to demonstrate a consistent effect of vitamin D supplementation on HDL levels (Ge et al., 2025; Lu et al., 2024). HDL metabolism is complex and influenced by genetic, dietary, and lifestyle factors, which may explain the absence of change in short-term interventions. While some observational studies have reported an association between vitamin D deficiency and

reduced HDL levels, supplementation trials have not consistently corroborated this relationship. This suggests that vitamin D's lipid-modifying potential may be limited to triglyceride-rich lipoproteins rather than HDL metabolism.

LDL-C exhibited a nuanced trajectory: both groups showed small numerical increases, yet the rise was more pronounced in the placebo arm, whereas the vitamin D group remained comparatively stable. This relative stabilization, though not statistically significant, may still be clinically relevant in prediabetic adults, as preventing further LDL elevation could help reduce cardiovascular risk. Meta-analyses have underscored considerable variability, with some trials documenting increases in LDL, others reporting reductions, and many observing no measurable effect (Ge et al., 2025; Lu et al., 2024; Mazidi et al., 2018). These inconsistencies underscore the context-dependent nature of vitamin D's impact on LDL metabolism, possibly influenced by baseline lipid status, adiposity, and genetic polymorphisms (Uitterlinden et al., 2004). Maintaining LDL stability, even without improvement, can represent a protective outcome in groups predisposed to atherogenesis.

The relatively short intervention duration likely limited the magnitude of lipid changes. Lipid metabolism responds slowly to nutritional interventions, and trials of longer duration or higher dosing have reported more pronounced effects (Mazidi et al., 2018). For example, studies extending beyond six months have demonstrated more consistent reductions in TG and LDL, suggesting that the modest improvements observed here may represent early trends rather than definitive outcomes. This highlights the importance of trial duration when evaluating micronutrient interventions in cardiometabolic risk.

Overall, the findings align with the mixed literature on vitamin D and lipid profiles. While some studies report improvements in TG and total cholesterol, others show null or inconsistent effects, particularly for HDL and LDL (Ge et al., 2025; Lu et al., 2024; Mazidi et al., 2018). This variability likely reflects differences in baseline vitamin D status, population characteristics, dosing regimens, and trial duration. Regional studies further support this heterogeneity, with Middle Eastern and European cohorts showing associations between vitamin D deficiency and dyslipidemia, but

inconsistent responses to supplementation (Al-Daghri et al., 2015). Genetic variability in vitamin D receptor (VDR) and binding protein (DBP) polymorphisms may also contribute to differential lipid responses (Uitterlinden et al., 2004).

Despite being modest, the lipid changes identified could have important clinical implications. Minor improvements in triglycerides and total cholesterol, along with steady LDL levels, may nonetheless translate into reduced long-term cardiovascular risk in prediabetic groups. Given the high burden of dyslipidemia in individuals with insulin resistance, vitamin D supplementation may serve as a low-cost adjunct to lifestyle interventions. However, the absence of major changes in HDL and the variability in LDL responses underscore the need for cautious interpretation. Longer trials, higher dosing, and stratification by baseline lipid status are required to clarify vitamin D's role in reducing cardiometabolic risk.

5.6 STRENGTHS AND LIMITATIONS

Strengths

1. **Dual-phase design**: Integration of a large cross-sectional study with an RCT allowed both prevalence estimation and mechanistic evaluation of vitamin D's therapeutic effects. This hybrid design bridged public health observation with clinical translation, especially valuable in resource-limited settings.

2. **Multidimensional biomarker profiling**: Comprehensive assessment of glycemic indices (FBS, 2HPP, HbA1c), insulin metrics (HOMA-IR, HOMA-B), FMD, and inflammatory markers (IL-6, hs-CRP) provided a nuanced understanding of vitamin D's role in cardiometabolic health.

3. **Real-world applicability**: Instructing participants to maintain their habitual lifestyles ensured that the observed changes could be attributed primarily to the pharmacological effect of vitamin D supplementation. This enhances external validity by showing how supplementation works under everyday conditions.

4. **Regional specificity and ethical rigor**: Conducted in Ibb Governorate, Yemen, the study addressed an underrepresented population with endemic hypovitaminosis D. Bilingual informed consent, culturally adapted protocols, and ethical approvals ensured participant comprehension and compliance, while demonstrating the feasibility of biomarker-driven research in resource-constrained environments.

5. **Seasonal context**: The trial coincided with autumn and winter, periods associated with elevated inflammatory markers due to infections. This contextual detail strengthens the interpretation of inflammatory outcomes and highlights the importance of seasonal adjustment in future studies.

6. **Sample size adequacy**: The study achieved a robust sample size that exceeded the minimum requirements for statistical power, ensuring reliable detection of primary outcomes. This methodological strength reinforced both the validity and the generalizability of the results, while also permitting robust subgroup analyses, including gender differences and potential genetic modifiers such as vitamin D receptor (VDR) polymorphisms.

7. **Consistency**: Another strength of this study lies in its consistency with findings from international and regional trials, reinforcing the external validity and situating our results within the broader scientific evidence base.

Limitations

1. **Short intervention duration**: 16 weeks may have been insufficient to capture long-term effects on HbA1c, insulin resistance, and systemic inflammation, which often require extended follow-up.

2. **Single-governorate design**: Conducted exclusively in Ibb Governorate, Yemen; findings may not be generalizable to other populations with different genetic, dietary, or environmental profiles.

3. **Seasonal and contextual influences**: Ramadan fasting, seasonal dietary shifts, and infection-related inflammation may have confounded glycaemic and immunological outcomes, attenuating between-group contrasts.

4. **Limited biomarker scope**: While glycaemic, vascular, and inflammatory markers were assessed, other relevant pathways (e.g., oxidative stress markers, adipokines, RAAS activity) were not measured, restricting mechanistic depth.

5. **Individual behavioral effects:** Some participants modified their behavior after learning their baseline health status. While this highlights the motivational impact of health awareness, it introduces a confounding factor: lifestyle changes may have contributed to outcomes alongside supplementation, making it harder to isolate the pure treatment effect.

CHAPTER VI

CONCLUSION AND FUTURE WORKS

6.1 OVERALL CONCLUSION

This doctoral investigation confirms the convergence of two major public health burdens in Yemen: the high prevalence of prediabetes (PreDM) and widespread vitamin D deficiency (VDD). Their coexistence underscores a dual vulnerability that accelerates progression to type 2 diabetes mellitus (T2DM) and cardiovascular disease.

Phase I established the epidemiological burden, revealing high rates of both PreDM and VDD, with women disproportionately affected due to sociocultural and biological determinants. Phase II demonstrated that high-dose vitamin D supplementation (50,000 IU/week for 16 weeks) produced measurable improvements in fasting glycaemia, β-cell function, and endothelial responsiveness. Although changes in HbA1c, insulin resistance, and lipid parameters were modest, stabilization of β-cell reserve and recovery of endothelial function highlight vitamin D's selective physiological targeting.

The paradoxical rise in inflammatory markers (IL-6, hs-CRP) in both groups, though attenuated in the vitamin D arm, illustrates the complexity of immunometabolic regulation. Collectively, the findings establish that correcting VDD in prediabetic individuals is not merely a nutritional intervention but a pragmatic strategy for metabolic and vascular health in resource-limited settings.

6.2 FUTURE RESEARCH DIRECTIONS

Building on the findings and limitations of this study, several avenues for future research are recommended to strengthen scientific understanding and inform public

health practice. Duration Longer supplementation periods are needed to determine whether the metabolic and vascular improvements can be sustained over time. An extended follow-up would allow assessment of progression to diabetes, long-term glycaemic stability, and cardiovascular outcomes. Future studies should be conducted across multiple regions of Yemen and the wider Middle East and North Africa to enhance external validity. Larger sample sizes will enable subgroup analyses by sex, age, severity of deficiency, and adiposity, providing a clearer picture of differential responses.

Structured measurement of dietary intake, physical activity, and sun exposure should be incorporated to reduce confounding and improve interpretability. Validated tools such as food frequency questionnaires, accelerometers, and sunlight exposure logs would allow more precise adjustment for behavioral influences. In addition, detailed immunological assessments, including cytokine panels, immune cell phenotyping, and gene expression analyses, are needed to clarify the paradoxical inflammatory responses. Genetic investigations focusing on variants of the vitamin D receptor and binding protein. could identify determinants of responsiveness and support precision nutrition strategies.

Future research should adopt standardized laboratory assays and external quality control programs to minimize biomarker variability and ensure reproducibility across sites. This will strengthen confidence in inflammatory and metabolic measurements. Beyond efficacy trials, implementation research is required to evaluate the feasibility, adherence, and cost-effectiveness of vitamin D supplementation programs in low-resource settings. Community-based interventions, school health initiatives, and integration into primary care workflows should be explored to translate clinical findings into scalable public health strategies. Future investigations should adopt multidisciplinary approaches, integrating endocrinology, nutrition, immunology, public health, and behavioral sciences. Studies must account for cultural practices, seasonal variation, and health system constraints to ensure findings are relevant, actionable, and translatable across diverse populations.

6.3 FINAL STATEMENT

Vitamin D supplementation emerges as a feasible, low-cost adjunct to reduce metabolic and vascular risk in prediabetic adults with baseline deficiency. By combining epidemiological characterization with randomized interventional evidence, this study establishes the dual burden of PreDM and VDD in Yemen and highlights the potential of targeted supplementation to improve glycaemic control, preserve β-cell function, and enhance endothelial responsiveness.

Vitamin D repletion should be viewed not only as nutritional correction but as part of a broader, biomarker-driven approach to non-communicable disease prevention. While challenges remain in sustaining long-term outcomes and addressing the complexity of inflammation, the evidence generated provides a strong foundation for precision public health strategies that are culturally sensitive, gender-aware, and contextually appropriate.

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APPENDIX A

QUESTIONNAIRE

Baseline characteristics of participants

Date:.....

Study Title :-	.....					
Particpant ID :-	.....					
Demographic Data	.....					
Body Hight	.....					
Age	< 18 years	☐	18 - 60 years	☐	> 60 years	☐
Weight Kg						
Height cm :-						
Sex	Male	☐	Female	☐		
Life style Factors :-						
Physical activity level	Low	☐	Moderate	☐	High	☐
Smoking status	Smoker	☐	Ex-smoker	☐	Non smoker	☐
Medical History						
Please indicate whether you hace neen diagnosed with the following condition :-						
D.M	Diabetic	☐	Non- Diabetic	☐		
Hypertention	Hypertention	☐	Non-Hypertention	☐		
Dyslipidemia	Yes	☐	Non	☐		
body weigth	< 50 kg	☐	> 50kg	☐		
Liver disease	Yes	☐	Non	☐		
Epilepsy	Yes	☐	Non	☐		
Tuberculosis { TB }		☐		☐		
Renal disease	Yes	☐	Non	☐		
M medicine	Yes	☐	Non	☐		
Anemia	Yes	☐	Non	☐		
Cancer	Yes	☐	Non	☐		
Medication and Supplements						
Are you currently taking Vitamin D supplements ?	Yes	☐	Non	☐		
Are you currently taking diabetes medications ?	Yes	☐	Non	☐		
Other regular medications { if applicable }	.....					
Additional Clinical information						
Pregnancy status { if applicable }	Yes	☐	Non	☐		
{Optional - Recommended for Vitamin D Studies }						
Average sun exposure per day	< 30 min	☐	30-60 min	☐	> 60 min	☐
Dietary intake of Vitamin D - rich foods	Low	☐	Moderate	☐	High	☐

Notes :

All information will be kept confidential and used for research purposes only

Please answer all questions as accurately as possible

APPENDIX B

SUBJECT INFORMATION SHEET

Phase 2

Research Title:

Exploring the link between vitamin D deficiency and prediabetes: prevalence and intervention strategies in Ibb Governorate, Yemen

Principal Investigator:

Norasyikin A. Wahab
Department of Medicine, Faculty of Medicine, UKM

Co-Investigator:

Mohammed Abdo Mohammed Yaseen Al-Hetar
Department of Medicine, Endocrine Unit, Faculty of Medicine, UKM

Purpose of the Study

This study aims to examine the effect of vitamin D supplementation on glycemic control and other relevant outcomes in individuals with prediabetes. The study employs a prospective cross-sectional survey and a randomized controlled single-blind trial design. Findings will contribute to understanding the potential role of vitamin D in managing prediabetes, insulin resistance, and inflammation. Results may also inform public health interventions in Yemen and similar settings.

Vitamin D deficiency is hypothesized to contribute to insulin resistance through several mechanisms, including:

- Increased pro-inflammatory cytokines
- Reduced insulin production by pancreatic beta cells
- Decreased glucose uptake in peripheral tissues

Study Procedures

If you agree to participate, you will be asked to attend two visits during the study period.

- **At each visit:**
    - Blood samples will be collected for glucose, insulin, vitamin D, and other relevant biomarkers
    - An endothelial function test will be performed (once at baseline and once at the end of Phase II)
    - You will complete a questionnaire about your health, diet, and lifestyle.
- **Intervention:**
    - Participants will be randomly assigned to two groups:
        - **Treatment group:** will receive a vitamin D supplement
        - **Placebo group:** will receive placebo tablets
- **Follow-up:**
    - After receiving the investigational product, no blood test will be performed until the end of Phase II.
    - After Phase II, all participants will undergo the same tests conducted at baseline.

- Additional visits may be required if unexpected adverse events occur.

Duration

The study will last approximately **4–6 months**, with each visit taking about **one hour.**

Risks and Benefits

- **Risks:** Minor discomfort may occur during blood collection, such as slight pain or bruising at the needle site.

- **Benefits:** Participants will receive free medical tests and vitamin D supplementation (if assigned to the treatment group). The study also contributes to scientific knowledge and potential community health benefits.

Voluntary Participation

Participation in this study is entirely voluntary. If you agree to take part, you will be asked to sign the **Informed Consent Form** and receive a copy of this Information Sheet.

You may withdraw from the study at any time without penalty, and your data will not be used. The researcher may also withdraw from the study if necessary (e.g., due to safety concerns or non-compliance).

Data and Confidentiality

All data collected will be kept strictly confidential. Only the research team and the UKM Research Ethics Committee (REC) will have access to the data. Results will be reported collectively, without identifying individual participants.

Payment and Compensation

There are no costs to you for participating in this study. You will not receive payment for participation.

Funding

This study is supported by a **UKM Research Grant**.

Contact Information

If you have any questions or concerns about the study, you may contact:

Principal Investigator:

Dr. Norasyikin A. Wahab
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APPENDIX C

SUBJECT INFORMATION SHEET IN ARABIC

نموذج معلومات المشارك

المرحلة الثانية

البحث: عنوان

استكشاف العلاقة بين نقص فيتامين د ومقدمة السكري: الشيوع واستراتيجيات التدخل في محافظة إب، اليمن

الرئيسي: الباحث

الدكتورة نوراسيكين أ. وهاب

قسم الطب، كلية الطب، جامعة كيبانغسان ماليزيا (UKM)

المشارك: الباحث

الدكتور محمد عبده محمد ياسين الهتار

قسم الطب، وحدة الغدد الصماء، كلية الطب، جامعة كيبانغسان ماليزيا (UKM)

هدف الدراسة

تهدف هذه الدراسة إلى فحص تأثير مكملات فيتامين د على التحكم في مستوى السكر في الدم وعلى مؤشرات أخرى ذات صلة لدى الأفراد المصابين بمقدمة السكري. تعتمد الدراسة على تصميم مزدوج يشمل دراسة مقطعية مستقبلية وتجربة سريرية عشوائية أحادية التعمية.

ستساهم نتائج هذه الدراسة في فهم الدور المحتمل لمكملات فيتامين د في إدارة مقدمة السكري، مقاومة الإنسولين، والالتهابات. كما قد تكون لهذه النتائج انعكاسات مهمة على استراتيجيات الصحة العامة في اليمن وفي بيئات مشابهة.

يُفترض أن نقص فيتامين د يؤدي إلى مقاومة الإنسولين عبر عدة آليات، منها:

- زيادة السيتوكينات الالتهابية
- انخفاض إنتاج الإنسولين من خلايا بيتا في البنكرياس
- انخفاض امتصاص الجلوكوز في الأنسجة الطرفية

إجراءات الدراسة

إذا وافقت على المشاركة، سيُطلب منك حضور **زيارتين** خلال فترة الدراسة.

- **في كل زيارة:**
  - سيتم أخذ عينات دم لقياس الجلوكوز، الإنسولين، فيتامين د، وعلامات بيولوجية أخرى.
  - سيتم إجراء اختبار وظيفة البطانة الوعائية (مرة عند البداية ومرة عند نهاية المرحلة الثانية).
  - ستُطلب منك تعبئة استبيان حول صحتك، نظامك الغذائي، وأسلوب حياتك.
- **التدخل:**
  - سيتم تقسيم المشاركين عشوائياً إلى مجموعتين:
    - **مجموعة العلاج:** تتلقى مكملات فيتامين د.
    - **مجموعة الضبط (الدواء الوهمي):** تتلقى أقراص وهمية.
  - يجب على جميع المشاركين الالتزام بتناول الأقراص وفق التعليمات.
- **المتابعة:**
  - بعد تلقي المنتج التجريبي، لن يتم إجراء فحوصات دم حتى نهاية المرحلة الثانية.
  - عند إتمام المرحلة الثانية، سيخضع جميع المشاركين لنفس الفحوصات التي أجريت في البداية.
  - قد تُطلب زيارات إضافية إذا ظهرت أحداث سلبية غير متوقعة.

مدة الدراسة

ستستمر الدراسة لمدة تتراوح بين **4 إلى 6 أشهر**، مع أن كل زيارة تستغرق حوالي **ساعة واحدة**.

المخاطر والفوائد

- **المخاطر:** قد يحدث ألم بسيط أو كدمات في موقع الإبرة أثناء أخذ عينات الدم.
- **الفوائد:** الحصول على فحوصات مجانية، تلقي مكملات فيتامين د (للمجموعة العلاجية)، والمساهمة في الفائدة العامة للمجتمع من خلال نتائج هذه الدراسة.

المشاركة الطوعية

المشاركة في هذه الدراسة طوعية بالكامل. إذا وافقت على المشاركة، سيُطلب منك توقيع **نموذج الموافقة المستنيرة** وستحصل على نسخة من هذا النموذج ومن ورقة المعلومات هذه.

يمكنك الانسحاب من الدراسة في أي وقت دون أي عقوبة، ولن تُستخدم بياناتك وسيتم التخلص منها. كما قد يقوم الباحث بسحبك من الدراسة لأسباب مختلفة مثل اعتبارات السلامة أو عدم الالتزام.

البيانات والسرية

سيتم التعامل مع جميع البيانات بسرية تامة. لن يتمكن من الوصول إليها سوى فريق البحث ولجنة أخلاقيات البحث بجامعة كيبانغسان ماليزيا (REC UKM). ستُعرض النتائج بشكل جماعي دون الإشارة إلى أي مشارك بشكل فردي، وبالتالي ستظل هويتك سرية.

الدفع والتعويض

لن تتحمل أي تكاليف للمشاركة في هذه الدراسة، ولن يتم دفع أي مقابل مالي للمشاركين.

التمويل

تُجرى هذه الدراسة بدعم من **منحة بحثية من جامعة كيبانغسان ماليزيا (UKM Research Grant)**.

لمن يمكنني التوجه بالسؤال؟

إذا كانت لديك أي أسئلة أو استفسارات حول الدراسة، يمكنك التواصل مع فريق البحث أو مع لجنة أخلاقيات البحث بجامعة كيبانغسان ماليزيا (REC UKM).

الباحث الرئيسي: الدكتورة نوراسيكين أ. وهاب
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الباحث المشارك: الدكتور محمد عبده محمد ياسين الهتار
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APPENDIX D

INFORMED CONSENT FORM

Research Title:

Exploring the link between vitamin D deficiency and prediabetes: prevalence and intervention strategies in Ibb Governorate, Yemen

Researcher's Name:

Norasyikin A. Wahab

I, ……

IC No. ……,

- confirm that I have read and understood the information provided in the Patient Information Sheet, including details regarding the potential risks of this study.
- I acknowledge that I have been given sufficient time to consider my participation and that all of my questions have been answered to my satisfaction.
- understand that I may withdraw from this study at any time, without providing a reason and without any negative consequences.
- understand that my anonymity and confidentiality will be maintained in all reports and publications arising from this study.

I hereby voluntarily agree to participate in this research study, to comply with the study procedures, and to provide the necessary information to the doctor, nurses, or other authorized staff members as requested.

Role	Name	Signature	IC Number	Date
Participant				
Witness (if any)				
Researcher				

APPENDIX E

INFORMED CONSENT FORM IN ARABIC

نموذج الموافقة المستنيرة

عنوان البحث:

استكشاف العلاقة بين نقص فيتامين د ومقدمة السكري: الشيوع واستراتيجيات التدخل في محافظة إب، اليمن

اسم الباحث:

نوراسيكين أ. وهاب

أنا، .....,

رقم الهوية .....,

- أؤكد أنني قد قرأت وفهمت المعلومات الواردة في ورقة معلومات المشارك، بما في ذلك التفاصيل المتعلقة بالمخاطر المحتملة لهذه الدراسة.
- أقر بأنني حصلت على وقت كافٍ للتفكير في مشاركتي وأن جميع أسئلتي قد تمت الإجابة عنها بما يرضيني.
- أفهم أنه يمكنني الانسحاب من هذه الدراسة في أي وقت، دون الحاجة إلى تقديم سبب ودون أي عواقب سلبية.
- أفهم أن هويتي وسريتي ستظل محفوظة في جميع التقارير والمنشورات الناتجة عن هذه الدراسة.

وبذلك، أوافق طوعاً على المشاركة في هذه الدراسة البحثية، والالتزام بإجراءاتها، وتقديم المعلومات اللازمة للطبيب أو الممرضين أو أعضاء الفريق المصرح لهم عند الطلب.

الدور	الاسم	التوقيع	رقم الهوية	التاريخ
المشارك				
الشاهد (إن وجد)				
الباحث				

APPENDIX F

PUBLICATIONS

Cureus
Part of SPRINGER NATURE

Open Access Original Article

The High Burden of Dyslipidemia in Ibb, Yemen: A Retrospective Analysis From 2018 to 2026 of Gender and Age Associations in 14,691 Individuals

Mohammed A.M.Y. Al-Hetar [1, 2], Norasyikin A. Wahab [3], Salah Al-Shawky [4], Abdullah Mohammed Al-Matary [5], Dhya'a Alhaq Mohammed Senan [6], Mohammad Alezzy [7], Malak M. Al-Hetar [8], Ahlam M. Asaber [9]

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Published 03/18/2026

DOI: 10.7759/cureus.105450

Abstract

Background: Dyslipidemia is a major modifiable risk factor for cardiovascular disease. Despite its global burden, data from Yemen remain scarce. This study aimed to determine the prevalence of lipid abnormalities and their associations with age, gender, and vitamin D deficiency among patients attending a specialized endocrinology and diabetes clinic in Ibb, Yemen.

Methods: We conducted a cross-sectional study of 14,691 individuals in Ibb, Yemen, using electronic medical records from the Medical City Complex (July 2018-January 2026). Demographic and lipid parameters were extracted, with categories defined by international guidelines. Statistical analyses were performed using appropriate parametric and non-parametric tests, with significance set at $p < 0.05$.

Results: A total of 14,691 patients were analyzed. Most had normal total cholesterol (85.2%), while borderline or high levels were more frequent in females. Triglyceride abnormalities were common, with nearly one-quarter showing high values (>199 mg/dL), slightly more in males. Low high-density lipoprotein cholesterol (HDL-C) was highly prevalent (72.9%), while high HDL-C was rare (0.9%). Low-density lipoprotein cholesterol (LDL-C) abnormalities were found in 8.6%, more frequently in females. Both gender and age were strongly associated with lipid variability ($p < 0.001$): females consistently exhibited higher total cholesterol, LDL-C, and HDL-C, whereas males had higher triglycerides. Middle-aged adults carried the greatest burden of abnormal triglycerides and LDL-C, while older adults were more prone to low HDL-C. Overall, gender and age emerged as the strongest determinants of dyslipidemia.

Conclusion: Lipid abnormalities are widespread in this Yemeni cohort, with low HDL-C and elevated triglycerides being the most prominent. Gender and age were the strongest determinants of lipid variability, underscoring the need for sex- and age-specific strategies in cardiovascular risk management. These findings align with international evidence and highlight the importance of tailored prevention policies in resource-limited settings.

Categories: Cardiology, Nutrition, Endocrinology/Diabetes/Metabolism
Keywords: age association, cardiovascular risk, dyslipidemia, gender differences, high-density lipoprotein (hdl), lipid profile, low-density lipoprotein (ldl), total cholesterol, triglycerides, yemen

Introduction

Dyslipidemia refers to abnormalities in serum lipid fractions, including total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). For this study, lipid categories were defined according to the Adult Treatment Panel III (ATP III) guidelines of the National Cholesterol Education Program (NCEP) [1]. Specifically, TC was classified as normal (<200 mg/dL), borderline (200-239 mg/dL), and high (≥240 mg/dL). TG was considered normal (<150 mg/dL), borderline (150-199 mg/dL), and high (≥200 mg/dL). LDL-C was categorized as optimal (<100 mg/dL), near-optimal (100-129 mg/dL), borderline high (130-159 mg/dL), and high (≥160 mg/dL). HDL-C was defined as low when <40 mg/dL in men or <50 mg/dL in women, with values ≥40 mg/dL (men) or ≥50 mg/dL (women) considered normal. These thresholds were consistently applied to classify participants and assess the prevalence of dyslipidemia [1]. These lipid disturbances are recognized as major modifiable risk factors for

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ANGIOTHERAPY RESEARCH

Prevalence, Predictors, and Gender-Based Risk Factors of Vitamin D Deficiency: A Retrospective Cross-Sectional Study

Mohammed a.m.y. Al-Hetar[1,2,4], Husni al-Goshae[3], Norasyikin a. Wahab[1], Mahfoudh A.M. abdulghani[3], Abdullah y. Al-Mahdi[3], Mohamad Faez Baobaid[3], Abdullah Mohammed al-matary[4], Qais m. Al-hetar[2], Mohammed e. Alezzy[2], Dya'a alhaq senan[2], Sakina Ruhi[3]

Abstract

Background: Vitamin D deficiency, a widespread global health issue, significantly impacts bone health and overall physiological well-being. Despite its prevalence, the deficiency often remains underdiagnosed and untreated, particularly in regions such as South Asia, the Middle East and North Africa (MENA), Europe, and the United States, where unique cultural, environmental, and lifestyle factors exacerbate its occurrence. Methods: This retrospective cross-sectional study, conducted at the Medical City Complex in Ibb, Yemen, analyzed data from 5,407 participants over six years (2018–2024). Serum 25-hydroxyvitamin D levels were measured to classify vitamin D status as deficient (<20 ng/mL), insufficient (20–29.9 ng/mL), or sufficient (≥30 ng/mL). Demographic and clinical characteristics were evaluated using descriptive statistics, independent t-tests, and multiple linear regression to assess age- and gender-based differences in vitamin D levels. Results: Among the study population, 77.1% were vitamin D deficient, with females showing a significantly higher prevalence (62.1%) than males (15.0%). Insufficiency was observed in 11.5%, and only 11.3% had sufficient levels. Males exhibited higher mean log-transformed vitamin D levels compared to females across all age groups. Deficiency rates peaked among adults aged 19–50 years, particularly females (45.24%). Regression analysis identified age and gender as significant predictors of deficiency, with older age and female gender increasing the likelihood of deficiency. Conclusion: Vitamin D deficiency remains alarmingly high in Yemen, particularly among females and adults aged 19–50 years. These findings emphasize the need for targeted public health interventions, including supplementation, dietary modifications, and strategies to increase safe sun exposure. Gender-specific approaches are crucial to mitigating the burden of vitamin D deficiency, particularly in populations at higher risk.

Keywords: Vitamin D deficiency, gender differences, prevalence, Yemen, public health

Significance | This study determined critical gender and age disparities in vitamin D deficiency, emphasizing targeted interventions for public health improvement.

Introduction

Vitamin D, a fat-soluble prohormone, plays a vital role in regulating calcium and phosphorus homeostasis, thereby maintaining bone health and overall physiological balance (Norman, 2008). Deficiency in vitamin D, or hypovitaminosis D, is recognized as a global public health issue with severe consequences such as rickets

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Please Cite This:
Mohammed a.m.y. Al-Hetar, Husni al-Goshae, Norasyikin a. Wahab, Mahfoudh A.M. abdulghani, Abdullah y. Al-Mahdi, Mohamad Faez Baobaid, Abdullah Mohammed al-matary, Qais m. Al-hetar, Mohammed e. Alezzy, Dya&#;a alhaq senan, Sakina Ruhi (2024). "Prevalence, Predictors, and Gender-Based Risk Factors of Vitamin D Deficiency: A Retrospective Cross-Sectional Study", Journal of Angiotherapy, 8(11),1-9,10042

CLINICAL EPIDEMIOLOGY & PUBLIC HEALTH RESEARCH

Demographic Patterns in Thyroid Dysfunction: Age and Gender Associations from a 7-Year Clinical Cohort in Ibb, Yemen

Mohammed A.M.Y. Al-Hetar [1,2,3*], Norasiykin A. Wahab[1,4], Malak Mohammed Al-Hetar[2], Nabil Al-joma'ai[5], Abdullah Ahmed Faleh[2], Adnan Taha Al-jaberi[6], Abdullah Almatary[3], Mohammad Ebraheem Alezzy[2], Eshtiak Mohammed[2], Ahd Hamoud Haidar[2], Mamoon Al-namer [5], Mohammed Alkhela [3]

Abstract

Background: Thyroid disorders, including overt and subclinical forms, are a major public health concern. Accurate biochemical classification is essential for early detection and effective management, particularly in population-based screening. **Objective:** To estimate the prevalence and distribution of thyroid dysfunction and examine age and sex associations using comprehensive hormone profiling. **Methods:** We conducted a retrospective cross-sectional study of 4,081 individuals evaluated at a tertiary endocrine center in Ibb, Yemen (August 2018–July 2025). Thyroid status was classified using FT3, FT4, and TSH. Subclinical hypothyroidism was defined as elevated TSH with normal FT3/FT4; subclinical hyperthyroidism as suppressed TSH with normal FT3/FT4. Abnormal TSH defined overt hypo- and hyperthyroidism with concordant FT3/FT4 changes. Analyses used SPSS v26 and Pearson's chi-square tests. The cohort comprised 92.4% females, with the majority aged 30–49 years. **Results:** Normal thyroid function was observed in 89.3% of participants. Subclinical hypothyroidism was present in 10.7%, subclinical hyperthyroidism in 2.7%, overt hypothyroidism in 0.8%, and overt hyperthyroidism in 1.7%. Females were disproportionately represented (92.4%), and the 30–49 year age group was most affected. Age showed a significant association with TSH in females (χ^2 = 10.303, df = 4, p = 0.036) and borderline significance in the total population (χ^2 = 9.418, df = 4, p = 0.051). FT3 and FT4 showed no consistent age associations. Sex did not consistently influence hormone profiles. **Conclusion:** Approximately 13.4% of the population exhibited subclinical thyroid dysfunction. Age was a significant determinant of TSH variation, particularly among women, underscoring the importance of age stratified screening and integrated FT3–FT4–TSH classification in endocrine surveillance.

Keywords: Thyroid dysfunction, subclinical hypothyroidism, subclinical hyperthyroidism, overt hypothyroidism, age association, gender, epidemiology, Ibb-Yemen.

1. Introduction

Thyroid disorders represent a diverse group of endocrine conditions arising from disturbances in hormone synthesis, secretion, or peripheral activity. This spectrum includes overt hypothyroidism and hyperthyroidism, their subclinical

Significance | This study highlights thyroid dysfunction demographics in Yemen, emphasizing age and sex impacts, guiding screening, interventions, and global endocrine comparisons.

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Journal of Clinical Medicine

MDPI

Systematic Review

Evaluating the Role of Vitamin D in Prediabetes Management, Insights from RCTs in the MENA Region: A Comprehensive Systematic Review

Mohammed A. M. Y. Al-Hetar [1,2], Noradliyanti Rusli [1], Mohd Amir Kamaruzzaman [3], Husni Al-Goshae [4], Wan Zurinah Wan Ngah [5,6], Shamsul Azhar Shah [7], Abdullah Mohammed Al-Matary [8], Qais Mohammed Al-Hetar [2], Dhya'a Alhaq Mohammed Senan [2] and Norasyikin A. Wahab [1,9,*]

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Abstract: Background/Objectives: The association between vitamin D deficiency and prediabetes has been extensively investigated, yet the findings remain inconsistent, with limited data available on the MENA region. This systematic review aims to assess the relationship between vitamin D deficiency and prediabetes in the Middle East and North Africa (MENA) region, focusing specifically on randomized controlled trials (RCTs). **Methods**: A comprehensive literature search was performed across four databases, which were Ovid MEDLINE, Cochrane, Scopus, and PubMed. RCTs studies conducted on people with prediabetes aged 15 years and older who live in the MENA region, and receiving vitamin D supplementation were included in the study. **Results**: From 2194 studies identified from the literature search, only 51 studies were considered eligible for full-text review. Ultimately, seven articles were finalized for inclusion. The findings from these studies showed mixed results, where some studies indicated that vitamin D supplementation had no significant effect on these outcomes. The remaining reported improvements in insulin sensitivity and a reduced risk of progression to type 2 diabetes with vitamin D supplementation. **Conclusions**: This systematic review examines the complex and contradictory relationship between vitamin D deficiency and prediabetes in the MENA region. Due to the mixed pattern seen in the intervention of vitamin D to prevent the development of type 2 diabetes, further research is necessary to elucidate the underlying mechanisms and potential confounding factors specifically in population of the MENA region.

Keywords: vitamin D; 25 hydroxy vitamin D; prediabetes; insulin resistance; MENA region; RCTs

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APPENDIX G

CONFERENCE

medicina

MDPI

Article

Undiagnosed Diabetes and Prediabetes in Yemen: A Growing Public Health Crisis in the Shadow of Conflict

Mohammed A. M. Y. Al-Hetar [1,2], Siti Liyana Saud Gany [3], Noradliyanti Rusli [4], Mohd Amir Kamaruzzaman [5], Wan Zurinah Wan Ngah [3,6], Shamsul Azhar Shah [7], Abdullah Almatary [8] and Norasyikin A. Wahab [1,9,*]

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Abstract

Background and Objectives: Type 2 diabetes mellitus (T2DM) is increasing in prevalence worldwide, placing a substantial burden on healthcare systems, particularly in resource-limited settings. In Yemen, limited screening and diagnostic capacity contribute to delayed detection and management. Prediabetes, a reversible state of dysglycemia, carries significant cardiovascular risk and frequently progresses to diabetes. Early identification of both conditions is vital for prevention and public health planning. *Materials and Methods:* This cross-sectional study, conducted from July 2024 to May 2025 in three medical centers in Ibb Governorate, Yemen, assessed 1045 adults aged 18–60 years without known diabetes or prediabetes. Glycaemic status was classified according to the 2025 American Diabetes Association criteria. Undiagnosed diabetes was defined using three diagnostic combinations: FBS + OGTT, FBS + HbA1c, and OGTT + HbA1c. *Results:* The prevalence of undiagnosed diabetes was 8.4% (FBS + OGTT) and 9.76% (FBS + HbA1c or OGTT + HbA1c). Prediabetes prevalence was 23.4%, 14.7% and 26.4% based on FBS, OGTT, and HbA1c, respectively. Females represented a higher proportion of undiagnosed diabetes and prediabetes cases. Age was significantly associated with glycemic status across all tests, while gender showed significant associations with FBS and HbA1c. Family history of chronic disease was significantly associated with HbA1c-based classification. Approximately 8–10% of adults in Ibb had undiagnosed diabetes, while up to one-quarter had prediabetes. Age and family history were key predictors of dysglycaemia. *Conclusions:* These findings highlight the need for targeted, multi-marker screening and early intervention strategies, particularly in relatively stable regions of conflict-affected settings, to prevent progression to diabetes and reduce long-term complications and healthcare burden.

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generally favourable if the tumour is completely resected and closely monitored.

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HIGH PREVALENCE OF PREDIABETES AND VITAMIN D DEFICIENCY IN IBB GOVERNORATE, YEMEN: A CROSS-SECTIONAL STUDY

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INTRODUCTION

Prediabetes and vitamin D deficiency are growing health concerns linked to diabetes progression and its complications, yet their prevalence and association remain underexplored, specifically in Yemen. This study aims to assess the prevalence of prediabetes and vitamin D deficiency among individuals in the Ibb Governorate, Republic of Yemen.

METHODOLOGY

A cross-sectional study involving 1046 participants who met study criteria recruited from various centres in the Ibb Governorate, Yemen, including Jiblah University for Medical and Health Sciences, Medical City Complex, and Al-Noor Hospital. They underwent HbA1c and level of vitamin D determination. Prediabetes was defined based on the American Diabetes Association, using HbA1c between 5.7% and 6.4%. Vitamin D levels of <20 ng/mL and 20-30 ng/mL are defined as deficiency and insufficiency, respectively.

RESULT

The prevalence of prediabetes was 25.7% (269). The mean HbA1c and age were 5.9 + 0.2 % and 41.4 + 10.2 years, respectively. From the prediabetes population, 71.4% (189) had vitamin D deficiency, while 20.7% (54) had vitamin D insufficiency, with a total of 93.1% (243) of prediabetes participants. The mean age for deficiency, insufficiency and sufficiency is 40.80 ± 9.9 ng/mL, 41.3 ± 10.0 ng/mL and 47.8 ± 9.0 ng/mL, respectively. The prevalence of low vitamin D levels (vitamin D deficiency and insufficiency) was slightly higher in males (126, 48.27%) compared to females (117, 44.83%). A significant age difference was observed for the sufficient group compared to both deficiency ($p = 0.01$) and insufficiency ($p = 0.04$) groups. The Chi-square test revealed a significant association between gender and the vitamin D status groups ($\chi^2 = 8.266$, $p = 0.01$).

CONCLUSION

The significant prevalence of prediabetes and vitamin D deficiency in the Ibb Governorate underscores the need for comprehensive interventions addressing both conditions. Correcting vitamin D deficiency may reduce the progression from prediabetes to diabetes, potentially improving metabolic health outcomes and mitigating associated complications.

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INSULIN INITIATION IN T2DM: OUTCOMES ON GLYCAEMIC CONTROL, BODY WEIGHT, AND HYPOGLYCEMIA RISK

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INTRODUCTION

The prevalence of diabetes in Malaysia is rising due to urbanization and socioeconomic changes. Despite evidence supporting good glycaemic control, maintaining optimal control remains challenging, with mean HbA1c levels ranging from 7.9% to 8.1%. Progressive beta-cell failure leads to secondary OAD failure, necessitating insulin therapy. This study evaluates the effect of a simple insulin therapy protocol on glycaemic control in T2DM patients with secondary OAD failure.

METHODOLOGY

A prospective study was conducted in outpatient clinics at Hospital Kuala Lumpur and Hospital Serdang. Patients with T2DM and secondary OAD failure (HbA1c >9%, fasting plasma glucose ≥9 mmol/L) were recruited. The intervention