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The Deficiency of Vitamin D and its Relationship with some Hormonal and Biochemical Parameters in Obese, Diabetic and Hyperprolactinemic Women in Maysan Province

A Thesis

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By

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بِسْمِ اللَّهِ ٱلرَّحْمَنِ الرَّحِيمِ

﴿ وَاللَّهُ أَخْرَجَكُم مِّن بُطُونِ أُمَّهَاتِكُمْ لاَ تَعْلَمُونَ شَيْئًا وَجَعَلَ لَكُمُ السَّمْعَ وَالأَبْصَارَ وَالأَفْئِدَةَ لَعَلَّكُمْ تَشْكُرُونَ ﴾

صدق الله العلي العظيم

سورة النحل، الآية (٧٨)

Supervisor's Certificate

I certify that this thesis entitled " **The Deficiency of Vitamin D and its Relationship with some Hormonal and Biochemical Parameters in Obese, Diabetic and Hyperprolactinemic Women in Maysan Province**" has been prepared under our supervision at the college of science, university of misan; as a partial fulfillment of the requirements for the degree of master of biology.

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Date: / /2025

Recommendation of Head of Biology Department

In view the available recommendations; I forward this thesis debate by examining committee**.**

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Date: / /2025

Dedication

I dedicate this work with deep gratitude and love to:

My beloved parents, whose prayers and guidance have always illuminated my path.

My brothers and sisters, for their kindness and continuous inspiration.

My friends, who taught me the true meaning of friendship.

Farah

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Farah

Summary

Summary

The current study aimed with investigate the relationship of vitamin D deficiency and some hormonal and biochemical parameters in obese, diabetic (type 2) and hyperprolactinemic women in Maysan province, its conducted in in some hospitals, Maysan specialized center for endocrine diseases and diabetes and some private laboratories, during the period from November 2023 with May 2025.

The whole sample is about 80 women (aged 30 - 40years), divided with four main groups (20 women / group), as following:

1- Control group (healthy women).

2- Obesity group (obese women).

3- Diabetes group (diabetic type 2 women).

4- Hyperprolactinemia group (hyperprolactinemic women)

The results revealed:

1- Vitamin D decreased significantly ($p \leq 0.01$) in different groups in comparison with control group.

2- Follicle stimulating hormone (FSH) and estradiol elevated significantly ($p \leq 0.01$) (except FSH elevated not significantly in hyperprolactinemia group) in different groups in comparison with control group.

3-Prolactin elevated significantly ($p \leq 0.05$) in obese and diabetic groups and ($p \leq 0.01$) in hyperprolactinemia group in comparison with control group.

4-Thyroid stimulating hormone (TSH) elevated significantly ($p \leq 0.01$), triiodothyronine (T3) elevated not significantly, thyroxine (T4) elevated significantly ($p \leq 0.01$) (except diabetic group elevated not significantly) in different groups in comparison with control group.

5-Insulin and C-peptide elevated significantly ($p \leq 0.01$) in obese and hyperprolactinemia groups and not significantly in diabetic group in comparison with control group.

6-Insulin resistance elevated significantly ($p \leq 0.01$) in obese and diabetic groups and significantly ($p \leq 0.05$) in hyperprolactinemia group in comparison with control group.

7- Glucose and glycated hemoglobin A1c (HbA1c) elevated significantly ($p \leq 0.01$) in diabetic group and not significantly in obesity and hyperprolactinemia groups in comparison with control group.

8-C-reactive protein (CRP) elevated significantly ($p \leq 0.01$) in different groups in comparison with the control group.

9-Calcium decreased not significantly in different groups in comparison with control group.

10-Alanine transaminase (ALT) elevated significantly ($p \leq 0.01$) in different groups in comparison with control group.

11-Aspartate transaminase (AST) elevated significantly ($p \leq 0.01$) in hyperprolactinemia group and elevated not significantly in obese and diabetic groups in comparison with control group.

12-Alkaline phosphatase (ALP) elevated significantly ($P \leq 0.05$) in obese and hyperprolactinemia groups and significantly ($p \leq 0.01$) in diabetic group in comparison with control group.

The functional impacts of these findings be analyzed via the effect of vitamin D deficiency that associated with different metabolic and inflammatory disturbances, leading with diverse detrimental influence on the hormonal and biochemical profiles of the studied groups.

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List of Abbreviations

Abbreviations	Equivalences
7-DHC	7- dehydrocholesterol
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AMH	Anti-müllerian hormone
ANOVA	One-way analysis of variance
AST	Aspartate transaminase
BMI	Body mass index
CRE	cAMP response elements
CRP	C-Reactive Protein
ER α	Estrogen receptor α
F.B.G	Fasting Blood Glucose
FGF23	Fibroblast growth factor 23
FSH	Follicle stimulating hormone
GnRH	Gonadotropin releasing hormone
HbA1c	Glycated hemoglobin A1c
HOMA-IR	Homeostatic model assessment for insulin resistance
HOXA10	Implantation gene
HPL	Hyperprolactinemia
hs-CRP	high-sensitivity C-reactive protein
IL	Interleukin
IL-1 RA	Interleukin -1 receptor antagonist
IL-1	Interleukin-1
IL-2	Interleukin-2
IL-6	Interleukin-6
LH	luteinizing hormone
NAFLD	Non-alcoholic fatty liver diseases
PCOS	Polycystic ovarian syndrome
RAAS	Renin–angiotensin–aldosterone system
RXR	Retinoid X receptor
T2DM	Type 2 diabetes mellitus
T3	Triiodothyronine
T4	Thyroxine
Th17	T-helper 17
TNF-α	Tumor necrosis factor alpha
IL-1 RA	Interleukin -1 receptor antagonist
TGF-β	Transforming growth factor beta
TRH	Thyrotropin-releasing hormone

TSH	Thyroid stimulating hormone
UVB	Ultraviolet radiation B
VDBP	Vitamin D binding protein
VDR	Vitamin D receptor
VDRE	Vitamin D response elements
WHO	World health organization

Chapter One

Introduction

Introduction

Vitamin D, known as a "sunshine" fat-soluble vitamin and considered as a prohormone steroid (Wimalawansa, 2018), is vital for the maintenance of bone and muscle health by promoting the absorption and metabolism of calcium and phosphate (Bendotti *et al*., 2025).

There are different vitamin D forms, such as D1, D2, D3, D4, and D5 according to their chemical structures that produced by sterol precursors ultraviolet exposure, these forms possessed the anti-osteoporotic and calcium regulatory activities (Komba *et al*., 2019; Kotake-Nara *et al*., 2021).

Both of D2 (ergocalciferol) plant-derived vitamin and D3 (cholecalciferol) animal derived vitamin are the most important vitamins for human biology, D3 is more effective in compared with D2 due to its high ability to bind with both vitamin D binding protein (VDBP) and vitamin D receptor (VDR) (Xie *et al*., 2020; Janoušek *et al*., 2022).

The presence of sunlight ultraviolet radiation B (UVB) contributes in pre-vitamin D formation from 7- dehydrocholesterol (7-DHC) in the skin, which is thermally isomerized and transformed to liver and kidneys to form an active metabolite of vitamin D (D3) that named calcitriol (1,25(OH)2D3) (Bikle, 2014).

Moreover, the physiological importance of vitamin D extends far beyond the regulation of calcium homeostasis and bone metabolism, controls both innate and adaptive immunity, cell proliferation, differentiation, apoptosis and secretion of some hormones including parathyroid hormone (PTH), insulin and fibroblast growth factor 23 (FGF23) (Zittermann and Gummert, 2010; Komaba *et al*., 2017; Wu *et al*., 2023).

The pleiotropic role of vitamin D in metabolism, inflammatory response, oxidative stress, modulation of cell growth and neuromuscular function reflects different distribution of vitamin receptors found in several organs and tissues throughout the body (Rosen *et al*., 2012; Medrano *et al*., 2018).

On the other hand, the deficiency of this vitamin has become a global pandemic and a public health concern that affects more than one billion of people and has contributed to multiple health complications, even in areas that receive adequate sunlight (Biasucci *et al*., 2024).

In addition, the deficiency may be results by inadequate both sunlight exposure and nutritional vitamin intake, vitamin absorption abnormalities, impairment the active metabolites conversion, life style habits, ethnicity and genetic polymorphisms (Vierucci *et al*., 2013).

Furthermore, this deficiency has been associated with numerous disorders, such as child's rickets, adult's osteomalacia/osteoporosis, cardiovascular diseases, arterial hypertension, dyslipidemia, cancer, multiple sclerosis, depression, dementia, psychiatric diseases, type 2 diabetes mellitus (T2DM) and obesity, however, the causative role of this deficiency remains unclear (Reid and Bolland, 2014; Milic *et al*., 2015).

Several studies demonstrated that vitamin D concentrations decreases with high amounts of body fat which associated with the overweight and obesity of individuals at different ages (Dominoni *et al*., 2022;Alzohily *et al*., 2024), furthermore, Sergeev (2012) indicated that the association of high amounts of adipose tissue with the deficiency of vitamin D might be attributed to the vitamin D eliminatory role of mature adipocytes by vitamin D3 and/or Ca2+ that mediated apoptosis, in addition, obesity might be reduced the bioactivity of vitamin D according to the inhibitive action of hepatic vitamin D 25-hydroxylase (Roizen *et al*., 2019).

Obesity, is one of the most important T2DM risk factors that causes insulin resistance and inflammation due to the accumulation of adipose tissue (Rohm *et al*., 2022).Vitamin D deficiency linked to predisposition of diabetes and may play a role in the development of diabetes (McCarthy *et al*., 2022), moreover, Rafiq and Jeppesen (2021) showed a strong relationship between vitamin D deficiency with insulin production and insulin resistance among T2DM patients , in addition ,vitamin D may have a beneficial effect on the action of insulin, either directly, by stimulating the expression of insulin receptors and thereby improving insulin responsiveness to glucose transport, or indirectly, through its role in the regulation of extracellular calcium and ensuring the influx of calcium through the cell membrane (Wu *et al*., 2023;Taneera *et al*., 2025).

In addition, different studies demonstrated that vitamin D deficiency is high prevalent in hyperprolactinemic women (Krysiak *et al*., 2020;Amanzholkyzy *et al*., 2023), furthermore, vitamin D found to be an amelioration action on the impact of the association between insulin resistance and high levels of prolactin in hyperprolactinemic patients (Krysiak *et al*., 2021), moreover, vitamin D supplementation decreased the prolactin levels due to its influence on calcium absorption in hyperprolactinemic rats (Sumaya and Saleh, 2023).

In view of this controversy, this study is an attempt to shed some light about the role of the deficiency of vitamin D and its relationship with some hormonal and biochemical parameters in obese, diabetic (type 2) and hyperprolactinemic women in Maysan province.

Aim of the study:

This study was conducted to investigate the following:

- **Hormonal Parameters**

Vitamin D

Follicle-stimulating hormone (FSH)

Estradiol

Prolactin

Thyroid-stimulating hormone (TSH)

Triiodothyronine (T3)

Thyroxine (T4)

Insulin

- **Biochemical Parameters**

Fasting blood glucose (F.B.G)

Glycated Hemoglobin A1c (HbA1c)

Insulin Resistance

C- peptide

Calcium

- **Pro-inflammatory Parameter and liver enzymes**

C-reactive protein (CRP)

Alanine transaminase (ALT)

Aspartate transaminase (AST)

Alkaline phosphatase (ALP)

Chapter Two

Literature Reviews

2.1 Vitamin D …... an overview

Vitamin D is a fat-soluble vitamin, considered as a pro-hormone (25(OH)D) of the secosteroid group due to its structure and functions that contributes to regulate various physiological processes within the human body (Khan *et al*., 2011). Moreover, vitamin D has many functions including phosphor–calcium homeostasis and bone mineralization, in addition, regulation of immune function, insulin secretion, muscle calcium transport, cell proliferation control, cell differentiation stimulation and apoptosis induction (Delanghe *et al*., 2015).

There are various forms of vitamin D, including D1, D2, D3, D4, and D5, which are distinguished by their distinct chemical structures, these forms are produced from sterol precursors upon exposure to ultraviolet radiation and possess anti-osteoporotic and calcium-regulatory activities (Komba *et al*., 2019; Kotake-Nara *et al*., 2021) (figure, 2.1), furthermore, the sun is accounts of the most one significant sources of vitamin D (80%) and vitamin D-rich foods (20%) (Holick and Hossein -Nezhad ,2017).

The precursor 7-DHC after exposure to UVB in mammalian skin cells produce the pre-vitamin D3 that attaching with highly specialized protein (vitamin D-binding protein DBP), in the liver, pre-vitamin D3 oxidize by 25-hydroxylase (CYP2R1) to converted to calcidiol or 25-hydroxy-cholecalciferol (25(OH)D3) the most prevalent and abundant metabolite form in the blood that lacks biological action (Dominguez *et al*., 2021) (figure , 2.2).

Pro-hormone (25(OH)D3) transported and oxidized in kidneys to 1,25-dihydroxyvitamin D (1,25-(OH)2D3), which is a biological active form of vitamin D by alpha-hydroxylase (CYP27B1) (Jones *et al*., 2012).

On the other hand, the conversion of the prohormone of vitamin D to its active form might be occurred in other different great majority of cells of the body that

contain the required enzymes for these processes (CYP27B1) (Adams and Hewison, 2012).

The two main forms of vitamin D including D2 (ergocalciferol), plant production source and D3 (cholecalciferol), mammalian skin cells production source (Kotake-Nara *et al*., 2021), moreover, D2 and D3 are transported through blood vessels by two ways, firstly: attaching with highly specialized protein (vitamin D-binding protein DBP), whose binding affinity ranges 85-90%, secondly: with albumin and lipoproteins, whose their binding affinity ranges 10 – 15 % or less (Xie *et al*., 2020).

Furthermore, D3 has proven to be the most potent form of human's vitamin D (Houghton and Vieth ,2006) according to the variance affinity of D2 and D3 toward their VDBP and receptor (Janoušek *et al*., 2022).

Vitamin D exert its action by two routes: firstly, the genomic effects that involved the interaction between vitamin D and its receptor , this interaction heterodimerizes with retinoid X receptor (RXR) that generates a complex of this interaction with RXR to binds with vitamin D response elements (VDRE) in order to activate the transcription of vitamin D-related genes (Spyksma *et al*., 2024), secondly, the nongenomic effects involved the binding of vitamin D with the membrane's VDR , this binding interacts with different membrane's proteins to activates the secondary messenger , then after to linked with VDRE to activate the transcription of vitamin D-related genes (Szymczak-Pajor *et al*., 2022) (figure , 2.3).

It is worth to note that vitamin D regulates more than 1000 genes around more than 200 tissues and cells within the human body (Van de Peppel and van Leeuwen, 2014).

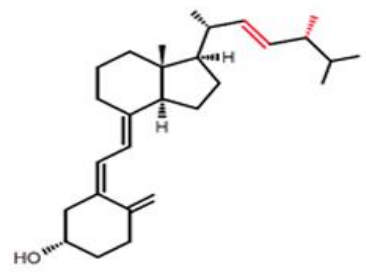
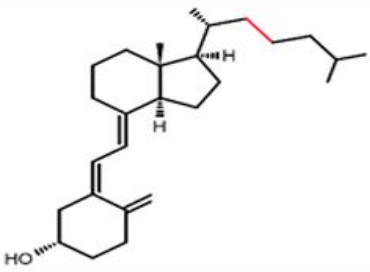
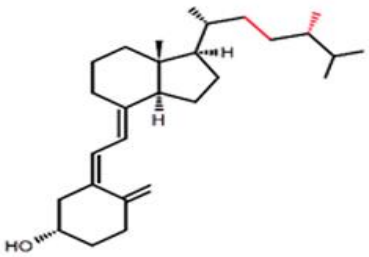
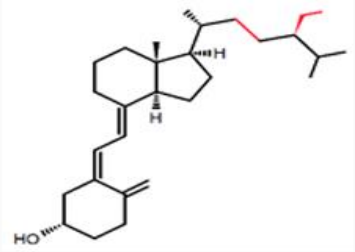
Vitamin D	Structure	Synonym	Sources
D_2		Ergocalciferol	Produced from ergosterol. Plants, fungi.
D_3		Cholecalciferol	Produced from 7-dehydrocholesterol. Fish, agriculture animals, dairy products, egg yolk, and skin of vertebrates.
D_4		22-dihydroergocalciferol, 22,23-dihydroercalciol	Produced from 22,23-dihydroergosterol. Mushrooms.
D_5		Sitocalciferol	Converted from 7-dehydrositosterol found in *Rauwolfia serpentine*

Figure (2.1): Natural analogs of vitamin D and their structures and sources (Szymczak-Pajor *et al*., 2022).

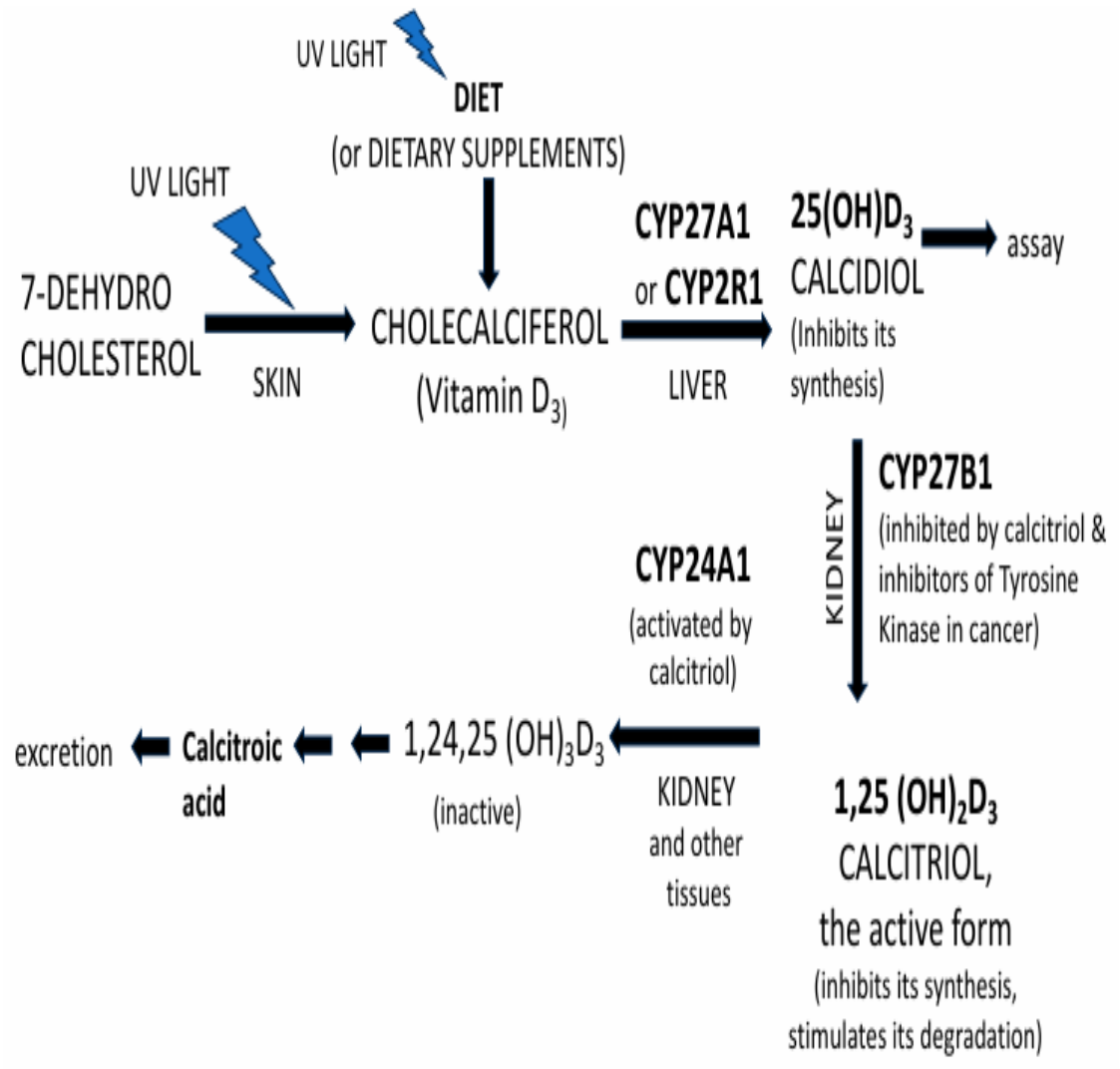


Figure (2.2): Schematic representation of vitamin D metabolism (Riccio, 2024).

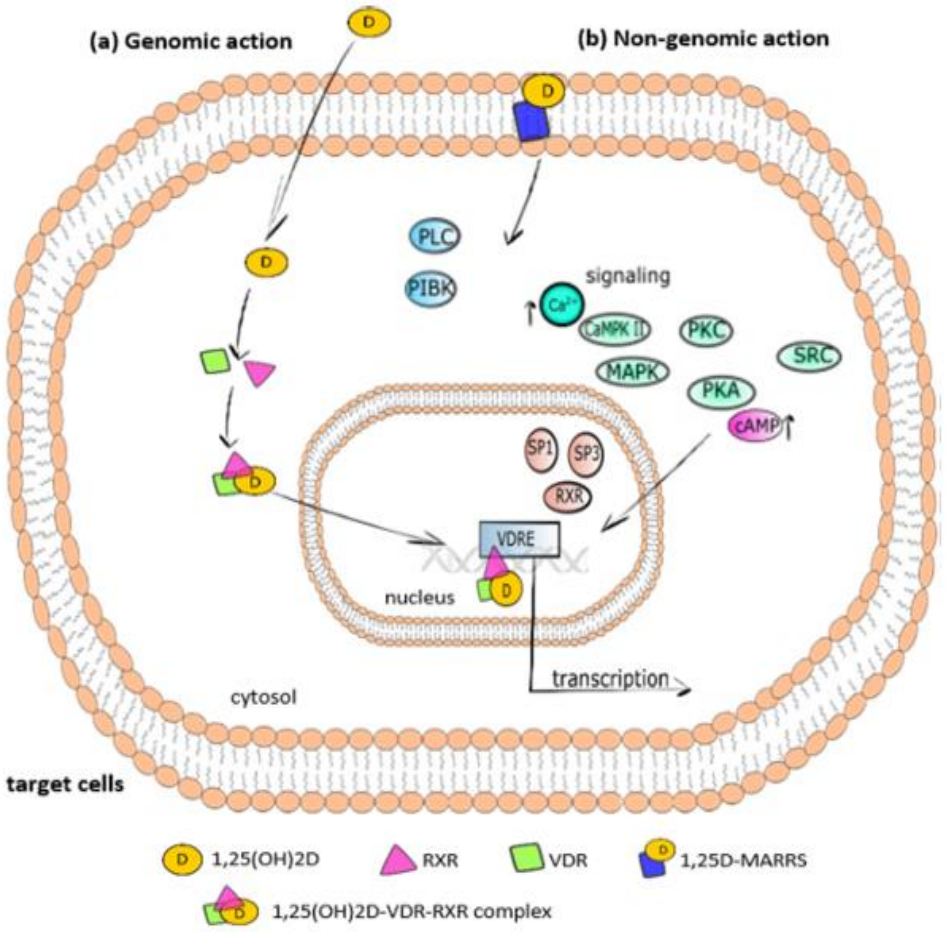


Figure (2.3): Summary of the cellular responses to vitamin D identified so far: (a) genomic and (b) non genomic pathways. Abbreviations: 1,25D-MARRS, 1,25D-membrane-associated rapid response steroid-binding protein; PI3K, phosphatidyl-inositol-3 kinase; MAPK, mitogen-activated protein kinases; PLC, phospholipase C; CaMPKII, Ca2+-calmodulin protein kinase II; PKC, protein kinase C; Src, nonreceptor tyrosine kinase Src; PKA, protein kinase A; cAMP, cyclic adenosine monophosphate; SP1 and SP3, transcription factors. ↑ increase; ↓ decrease. (Szymczak-Pajor *et al*., 2022).

2.2 Vitamin D deficiency

Vitamin D deficiency is a global health problem due to its worldwide high prevalence and adverse clinical consequences, that threatens more than one billion individuals around the world (Biasucci *et al*., 2024), has reached pandemic proportions globally, documented across different age groups and ethnicities (Al Amiry and Shahwan, 2020), ranges 24% - 49% of the global population (Cashman, 2022).

The definition of this deficiency based on the serum 25(OH)D value that reflects the natural synthetic vitamin D and/or food and supplements vitamin origin (Seamans and Cashman ,2009), moreover, the values of vitamin D less than 50 nmol / L or 20 ng/ml considered as deficiency of this vitamin and values range 20–29.9 ng/ml as insufficiency (Chedid *et al*.,2025).

This deficiency may results from inadequate exposure to sunlight, insufficient nutritional vitamin intake, personal characteristics (such as skin pigmentation, sunscreen usage, working environment, outdoor physical activity and sun exposure behavior) (Rosecrans and Dohnal, 2014) and age-related declines in dermal synthesis of vitamin by diminishing rate of hydroxylation and poorer response of target tissues (WHO,2005).

On the other hand, the risk of vitamin deficiency may be elevated in some certain medical conditions such as intestinal malabsorption, liver and renal insufficiencies (Cashman, 2020), fat malabsorption syndromes, bariatric surgery (Holick *et al*., 2011), short bowel syndrome (Sinha *et al*., 2013).

Deficiency of vitamin D has also been shown to be associated with mortality risk increase (Wang *et al*., 2023), the insufficiency levels of 25(OH)D might be behind of all-cause mortality (Durup *et al*., 2012).

Vitamin D deficiency has detrimental skeletal effects, including osteomalacia, high bone turnover, bone loss and an increase risk of hip fractures in elderly

people (Bouillon *et al*., 2019) and related with hyperparathyroidism that contributed in least extent of the pathophysiology of bone loss and fracture risk among severely vitamin D-deficient individuals (Yedla *et al*., 2023).

Furthermore, Abed and coworkers (2024) observed that vitamin D deficiency potentially leads to insufficient insulin levels via disturbing both of synthesis and secretion of insulin that accelerated the development of metabolic syndrome such as obesity and T2DM, moreover, this deficiency found to be a accompanied with an excessive body weight due to the role of vitamin D in regulation of adipogenesis (Nimitphong *et al*., 2020).

Moreover, the deficiency increases the incidence of cardiovascular disorders, risk of hypertension, atherosclerosis, inflammation and diabetes mellitus (Aggarwal *et al*., 2016).

Deficiency may predispose to hypertension through upregulation of the renin–angiotensin–aldosterone system (RAAS) and increased both vascular resistance and vasoconstriction (Chen *et al*., 2015), due to the role of 1,25(OH)2 D as a down-regulates renin gene transcription by suppressing, at least in part, cAMP response elements (CRE) - mediated transcriptional activity in the renin gene promoter (Yuan *et al*., 2007).

Vitamin D deficiency has been associated with endothelial function impairment and vascular stiffness, which are known predictors of long-term cardiovascular morbidity and mortality (Dalan *et al*., 2014).

Furthermore, vitamin D is involved in the maintenance of immune system homeostasis and dampens autoimmune responses via modulation of T cells, B cells, monocyte/macrophage and dendritic cells (Sîrbe *et al*., 2022),in addition, vitamin D has shown potent immunomodulatory effects and plays important roles in the pathogenesis of autoimmune diseases (Mele *et al*., 2020),the deficiency of this vitamin associated with autoimmune diseases such as multiple sclerosis,

inflammatory bowel disease and rheumatoid arthritis (Wu *et al*., 2022; Hysa *et al*., 2024; Balasooriya *et al*., 2024).

Vitamin D can inhibit inflammation and immune reaction, promote synthesis and secretion of insulin and increase insulin sensitivity (Argano *et al*., 2023), and its deficiency may have a role in the pathogenesis of diabetes type 1 but cannot be the sole determining factor for the development of this disease (Almansour *et al*., 2025).

Vitamin D deficiency is associated with an increase risk of major depression and anxiety (Casseb *et al*., 2019), vitamin D has been describing as a potential strategy for the prevention and or depressive symptoms treatment (Wang *et al*., 2016).

Vitamin D deficiency activates the ageing process and initiates the onset of the age-related diseases such as a decline in cognition, depression, osteoporosis, hypertension and cardiovascular diseases, diabetes, cancer, muscle weakness and Alzheimer's disease (Banerjee *et al*., 2015; Wang *et al*., 2017), due to the role of vitamin D in promoting the activity of autophagy that acts to slow down the ageing processes (Berridge, 2017).

It has been found that vitamin D deficiency associated with a high prevalence of cancers such as breast (Rosso *et al*., 2023), colon (Lu *et al*., 2012) and prostate cancers (Erzurumlu *et al*., 2023), it also contributes with the progression of numerous cancers due to the role of this vitamin in cell cycle regulation, cellular proliferation, apoptosis and molecular cell signaling (Fleet *et al*., 2012).

Moreover, deficiency is associated with adverse fertility outcomes including polycystic ovarian syndrome (PCOS) and hypogonadism (Trummer *et al*., 2018), in addition to lower pregnancy rates (Polyzos *et al*., 2014), especially, vitamin D is necessary in implantation process via it is role in regulation expression of HOXA10 (implantation gene) (Daftary and Taylor, 2006).

Deficiency remains prevalent among pregnant women around the world with consistent evidence suggesting an incidence of 51% to 100% in developing countries (Van der Pligt *et al*., 2018) and related with pregnancy complications such as preeclampsia, gestational diabetes mellitus, hypertension, underdeveloped fetuses and vitamin D deficient newborns (Karras *et al*., 2020).

2.3 Vitamin D deficiency related with reproductive and thyroid hormones

Vitamin D plays a critical role in reproductive process via its receptors and related enzymes and that spread in all male and female reproductive tissues (Lorenzen *et al*., 2017).

High percent of infertile men has a deficient of vitamin D and reveled one or more different semen abnormalities (Kumari *et al*., 2021), this infertility caused by testicular weight reduction, put off maturation of seminiferous tubules and sperm quality impairment in male rats (Fu *et al*., 2017).

Similarly, high percent of vitamin D deficiency is prevalent during the women's reproductive age, this deficiency associated with the disruptions of steroidogenesis and related with premenstrual syndrome, dysmenorrhea and early menarche (Luk *et al*., 2012; Baird *et al*., 2013).

Vitamin D may promote differentiation and development of follicles via the activation of granulosa cells VDRE that changing FSH sensitivity and allowing the latter to binds with its receptors and initiates the aromatization process (Irani and Merhi, 2014; Gandhari *et al*., 2023).

Xu and coworkers (2019) showed that high levels of FSH associated with vitamin D deficiency which is a marker of ovarian reserve, suggesting that this deficiency may plays a role in diminishing of this ovarian reserve (Nikbakht *et*

al., 2024), additionally, Jukic and his coworkers (2015) demonstrated that the relationship between vitamin D deficiency and elevated FSH levels in premenopausal women may have a detrimental effect on ovarian reserve, moreover, Bacanakgil and his coworkers (2022) found that FSH levels increased in women with insufficiency ovarian reserve and decreased after the supplementation of vitamin intake , therefore vitamin D might be considered as a fertility treatment for the reduction of the ovarian reserve.

Similarly, this deficiency correlated with high levels of luteinizing hormone (LH) in women during their reproductive age (Bharti and Singh ,2023) and these levels of LH decreased in PCOS women after vitamin D intake (Kazeminia *et al*., 2024).

Furthermore, authors found that vitamin D is more necessary for the regulation of estrogen synthesis (Kinuta *et al*., 2000), in addition, estradiol levels increased in deficient women and declined after the vitamin supplementation intake (Grzechocińska *et al*., 2018; Donayeva *et al*., 2023). However, it is not clear that how this supplementation interferes with estrogen availability due to its role of estrogen synthesis induction and\or inhibition in animals (Hong *et al*., 2017) and humans (Merhi *et al*.,2014).

Vitamin D deficiency correlated with high levels of prolactin in adolescent girls (Amanzholkyzy *et al*.,2023) and vice versa Awad and Ismail (2017) which mentioned that high levels of prolactin inhibit the enzyme required (25-hydroxylase) for the D3 synthesis.

Vitamin D deficiency was high prevalence in hypothyroidism patients, a negative correlation between serum vitamin D levels and TSH levels, while a positive correlation with both FT3 and FT4 in women (Mustafa *et al*., 2022), in addition, similar findings be observed by Nar and Avcı (2020), they found a significant positive correlation with FT3 and FT4 in premenopausal women,

moreover, Modi and Garg (2024) observed a significant association between vitamin D deficiency and the presence of thyroid disorders in women of reproductive age. Moreover, an inverse relationship has shown between vitamin D deficiency and the occurrence of autoimmune thyroid diseases (Karakaya *et al*., 2025).

Furthermore, Talaei and his colleagues (2018) reported that vitamin D intake caused an independent reduction in serum TSH levels separately no significant changes in T3 and T4 in women with primary hypothyroidism, the same result were obtained in in Hashimoto's thyroiditis women (Chahardoli *et al*., 2019)

It is worth to note, the interaction between both of vitamin D and the thyroid gland is believed to be reciprocal according to their binding with same receptors steroid hormone receptors (Jubair *et al*., 2021).

Vitamin D levels might influence hypothalamus–pituitary–thyroid axis, via VDR expression on the hypothalamus and thyrotropic pituitary cells means and by exerting a direct effect on thyrocytes, which become less responsive to TSH stimuli leading to high levels of TSH (Barchetta *et al*., 2015), furthermore, women with vitamin D deficiency more susceptible to impaired sensitivity to thyroid hormones (Zhou *et al*., 2023).

On the other hand, the relationship between vitamin D and thyroid hormones is unclear and controversial due to many studies showed either positive (Verrusio *et al*., 2019), negative (Mansorian *et al*., 2018) or no associations (Zhang *et al*.,2014).

2.4 Vitamin D deficiency related to liver enzymes

The liver is a key metabolic center for metabolism and performs numerous functions, including carbohydrate metabolism, glycogen storage, lipid metabolism, urea synthesis, plasma protein secretion and bile production (Tanimizu and Miyajima, 2007).

Liver enzymes including : Alanine transaminase (ALT) is an enzyme that is found primarily in hepatocytes (lower concentrations in cardiac, renal, and muscle tissue) and thus is specific to the hepatocellular injury, Aspartate transaminase (AST) is an enzyme found in the liver and also in other sites such as skeletal muscle, cardiac muscle, renal tissue and brain, Alkaline phosphatase (ALP) is an enzyme that is primarily found in the hepatobiliary tract, bone, placenta and to a smaller extent in intestinal tissue , these enzymes are used in the evaluation of liver function (Kalas *et al*., 2021).

The relationship between vitamin D and the liver function may be attributed to both of the prevalence of vitamin D receptors and conversion of pre-vitamin D to 25(OH)D in the liver cells (Zúñiga *et al*., 2011).

Many studies showed that vitamin D deficiency associated with high levels of ALT and AST in women (Bahreynian *et al*., 2018; Kayacan *et al*., 2019), in addition, Skaaby and his coworkers (2014) mentioned that vitamin D deficient women tended to having high levels of liver enzymes also found an inverse association between vitamin D deficiency and the prevalence of hepatic disorders. Moreover, vitamin D deficiency is considered an independent risk factor for the liver enzymes increase and the occurrence of liver diseases (Namakin *et al*., 2021).

Different studies demonstrated that ALP levels increase in women with vitamin D deficiency (He *et al*., 2020; Rajab, 2022), in addition, Bellastella and his colleagues (2021) found a significant negative correlation between levels of vitamin D and ALP, suggested that ALP might be involved in the regulation of vitamin D-25-hydroxylase activity.

On the other hand, vitamin D deficiency is common among patients with liver diseases due to fat malabsorption, deficiency of bile salts, impaired hepatic hydroxylation of vitamin D and reduced hepatic production of vitamin D binding protein (Malham *et al*., 2011).

Vitamin D deficiency was also shown to be associated with elevated ALT and AST levels in women that attacked for long time by non-alcoholic fatty liver diseases (NAFLD) (Hamed *et al*., 2022), and in newly diagnosed NAFLD women, this deficiency increases the incidence of NAFLD (Kumar *et al*., 2023),moreover, vitamin D deficiency closely relates to the severity of this disease due to is implicated in the pathogenesis of insulin resistance which is a key factor in the development of NAFLD (Kitson and Roberts, 2012).

Many studies showed that vitamin D deficiency associated with metabolic syndrome which consider a risk factor for increase liver enzymes and development of NAFLD (Borges-Canha *et al*., 2021; Ebrahimpour-Koujan *et al*., 2024), moreover, vitamin D deficiency might be considered as a marker for NAFLD diagnosis (Cai *et al*., 2020).

Furthermore, vitamin D prevents fat accumulation in the liver by inhibiting lipogenesis and regulating the circulation of free fatty acids (Mahmoudi *et al*., 2021).

Vitamin D acts as an "immune-modulator" to prevent liver cirrhosis by suppressing fibroblast proliferation and collagen production (Artaza and Norris, 2008), moreover, Abramovitch and his colleagues (2011) confirmed the anti-fibrotic effects of vitamin D through inhibition of hepatic stellate cells proliferation in an in vivo murine model.

Vitamin D supplementation decreases ALT and AST levels in women with NAFLD (Al-Bayyari *et al*., 2021). In similar manner, Amiri and his coworkers (2017) mentioned that the long-term of vitamin D intake has an anti-fibrotic and anti-inflammatory role that improves liver enzymes in NAFLD women, in addition, Tavakoli and his coworkers (2019) mentioned that a high dose of

vitamin D supplementation was associated with a reduction in serum ALT and AST in girls who had abnormal liver function tests.

2.5 Vitamin D deficiency related with obesity

Obesity is an abnormal or excessive accumulation of body fat, resulting from an imbalance between energy intake and expenditure (Duan *et al*., 2020), more than 1.9 billion adults and 650 million were overweight and obese respectively (WHO, 2021), currently, the mechanism of obesity is not fully understood, it is generally acknowledged that the interaction of genetic and environmental factors contributes to the occurrence of obesity (Lin and Li , 2021), the etiology of obesity is largely influenced by environmental variables, such as lifestyle, eating habits, physical activity and other environmental factors (Sharma *et al*., 2020), coupled with hypertrophy of adipose tissue (Ghaben and Scherer, 2019),disorders in glucose and lipid metabolism (Morigny *et al*., 2021) and increased inflammatory responses within adipose tissue (Reilly and Saltiel ,2017).

The most noteworthy is that obesity is a driver of dyslipidemia, hypertension, metabolic syndrome and a wide range of chronic cardiometabolic diseases, including T2DM and cardiovascular diseases (Sharma *et al*., 2021).

On the other hand, the connection between vitamin D deficiency and obesity has become more prevalent as a result of the identification of 25(OH)D3 deficiency in obese people (Nikolova and Agovska, 2024), moreover, this deficiency may be a hidden cause of the metabolic syndrome and obesity (Ergul *et al*., 2023), in addition, many studies suggest that vitamin D deficiency is associated with a strong prevalence of obesity in children (Zhu *et al*., 2025), adults (González-Molero *et al*., 2013) , elderly men and women (Răcătăianu *et al*., 2018), therefore, insufficient vitamin D intake may be predicted obesity and metabolic syndrome later (Gagnon *et al*., 2012).

Vitamin D has a negative and significant correlation with several factors such as BMI, total fat mass, subcutaneous and visceral adiposity and waist circumference in obese women (Walsh *et al*., 2016)**,** moreover, De Oliveira and his colleagues (2020) demonstrated that obesity decreases the response to vitamin D supplementation in adult women.

It's noteworthy that the relationship between vitamin D and obesity is considered bidirectional, on one hand, obesity is considered a condition associated with vitamin D deficiency and on the other hand, vitamin D deficiency is associated with an increased risk of obesity (Bennour *et al*., 2022).

Moreover, vitamin D has a direct impact on BMI (Rafiq and Jeppesen, 2018) thereby, 1.3 nm/L decrease in vitamin D can increase BMI by 1 kg/m2(Stein *et al*., 2009), in addition, the concentration of vitamin D seems to be higher in lean compared to obese individuals, dilution of ingested or cutaneously synthesized vitamin D in the large fat mass is the potential reason behind inverse relationship with BMI (Walsh *et al*.,2017), moreover, seasonal variations and vitamin D supplementation confirmed that dilution of vitamin D is the main reason for lower vitamin D levels in obese people compared to normal-weight people (Vranić *et al*., 2019).

Furthermore, vitamin D deficiency might be occurred in obese people due to the sequestration of this vitamin by fat tissue and a decrease its ability to convert pre-vitamin into vitamin in the skin (Risanti *et al*., 2023), in addition, sequestration of vitamin D refers not only to its hydrophobic nature and tendency to dissolve in adipose tissue but also refers to their inability to regress into the circulation as a substrate for liver 25-hydroxylas (Derbel *et al*., 2024).

Moreover, vitamin D receptors and vitamin D-metabolizing enzymes that produce 25(OH) D and 1,25(OH)2D are expressed in human adipose tissue (Ruiz-Ojeda *et al*., 2018),in addition, vitamin D plays a role in the regulation of lipolysis and adipogenesis (Abbas, 2017), moreover, vitamin D is involved in adipogenesis

by suppresses the activity of the key adipogenic transcription factor, thereby reduces the accumulation of the lipids in the adipocytes (Clemente-Postigo *et al*., 2015).

Furthermore, vitamin D may contribute to the maintenance of body weight and promotion of weight loss due to its role of the remodeling of adipose tissue by apoptotic Ca2+ signaling and the removal of mature adipocytes, this removal is supported by 1,25(OH)2D/Ca2+-mediated apoptosis (Sergeev,2012).

VDR is expressed in both the pancreatic β-cells and the adipocytes, suggesting the involvement of vitamin D in glucose homeostasis and fat metabolism (Jamka *et al*., 2015), in addition, vitamin D has an important role to prevent the risk of glucose intolerance, this vitamin exhibits a hypoglycemic function, which is justified by stimulating the expression of insulin receptors on the cell membrane and through increasing insulin secretion by pancreatic cells (Szymczak-Pajor and Sliwinska,2019).

Moreover, vitamin D deficiency could potentially lead to insufficient insulin levels by disturbing insulin synthesis and secretion, and accelerate the obesity (Nam *et al*., 2012), in addition, vitamin D deficiency is involved in the production of inflammatory cytokines that caused an insulin resistance and leading to metabolic syndrome (Ozkan , 2019) , on the other hand , the anti-inflammatory effect of vitamin D may have a role in the improvement of insulin sensitivity in patients with relatively higher BMI (Fenercioglu , 2024).

Furthermore, many studies reported that vitamin D was inversely associated with homeostasis model assessment of insulin resistance (HOMA-IR), the power of this association was linked with the high BMI (Rafiq and Jeppesen 2021; Mirza *et al*., 2022), in addition, Schleu and his coworkers (2021) found that obese women with vitamin D deficiency tended to appear higher values of insulin and HOMA -IR.

Furthermore, insulin sensitivity and secretion may be enhanced by vitamin D by two ways directly stimulating the expression of insulin receptors and/or by activating peroxisome proliferator-activated receptor, (a factor implicated in the regulation of fatty acid metabolism in skeletal muscle and adipose tissue), indirectly via its role in regulating extracellular calcium concentration and flux through cell membranes in the beta cells and peripheral insulin-target tissues (Dunlop *et al*., 2005).

In addition, vitamin D-deficient obese women had high levels of HOMA-IR that decreased after vitamin D intake , therefore, supplementation with vitamin D may be more beneficial for people whom have high insulin resistance (Rashad *et al*.,2023), similarly, Imga and his team (2019) showed that vitamin D supplementation reduces both insulin and HOMA-IR levels in obese women and they observed that for each of 1 ng/ml increase of serum levels 25(OH)D is equivalent to a 0.30-fold reduction in HOMA-IR value.

Moreover, vitamin D-deficient obese pregnant women are predisposed to different glucose and lipid metabolic disorders that increase the risk of obesity and diabetes for offspring in later life (Alhomaid *et al*., 2021).

Vitamin D deficiency and obesity seem to affect negatively female fertility (Bosdou *et al*, 2019), moreover, Rajbanshi and his team (2023) indicated that vitamin D was negatively associated with levels of estrogen in obese PCOS women, in addition, Viana Pires and his colleagues (2020) mentioned that 25(OH)D levels are associated inversely with FSH and estradiol levels in adolescent obese girls.

Moreover, Zhou and his colleagues (2016) indicated that vitamin D deficiency associated inversely with TSH levels in obese women, in addition, Safari and his colleagues (2023) mentioned that vitamin D supplementation improves serum TSH in obese women with hypothyroidism.

Moreover, obese women with deficient vitamin D revealed a high risk of hepatic steatosis and a negative association with high levels of ALP (He *et al*., 2020), ALT and AST (Esteghamati *et al*., 2014), in addition, vitamin D supplementation reduces the levels of ALT and AST in obese women (Amiri *et al*., 2016; Hussain *et al*., 2019).

2.6 Vitamin D deficiency related with diabetes type 2

Many studies have provided strong support for the inverse relationship between vitamin D deficiency and the risk of developing T2DM (Vijay *et al*., 2023; Gul *et al*., 2024).

Vitamin D deficiency is associated with the induction and development of diabetes due to vitamin D having a beneficial effect on insulin secretion, insulin tolerance, and beta-cells function (Szymczak-Pajor and Sliwi ´nska, 2019), vitamin D regulates insulin secretion of pancreatic β-cells through the binding of vitamin D complex with VDRE to expressed about the insulin receptor and thereby the secretion of insulin (Bland *et al*., 2004;Wu *et al*., 2023) (figure , 2.4).

Furthermore, impaired insulin secretion and glucose intolerance occur after targeted disruption of VDRs or vitamin D-activating enzymes in various animal knock-out models (Lontchi-Yimagou *et al*., 2020).

Vitamin D appears to exert its anti-diabetic effect via three routes: firstly, modulation of both hepatic glucose and lipid metabolism, secondly, improves insulin sensitivity via stimulating insulin receptors , and thirdly, via the effects of pancreatic β-cells VDR signaling on glucose-stimulated insulin biosynthesis and release (Leung, 2016;Wu *et al*., 2023), in addition, vitamin D supplementation initiated a mark improvement of tissue insulin sensitivity when used among a population of patients suffering from metabolic syndrome (Nazarian *et al*., 2011).

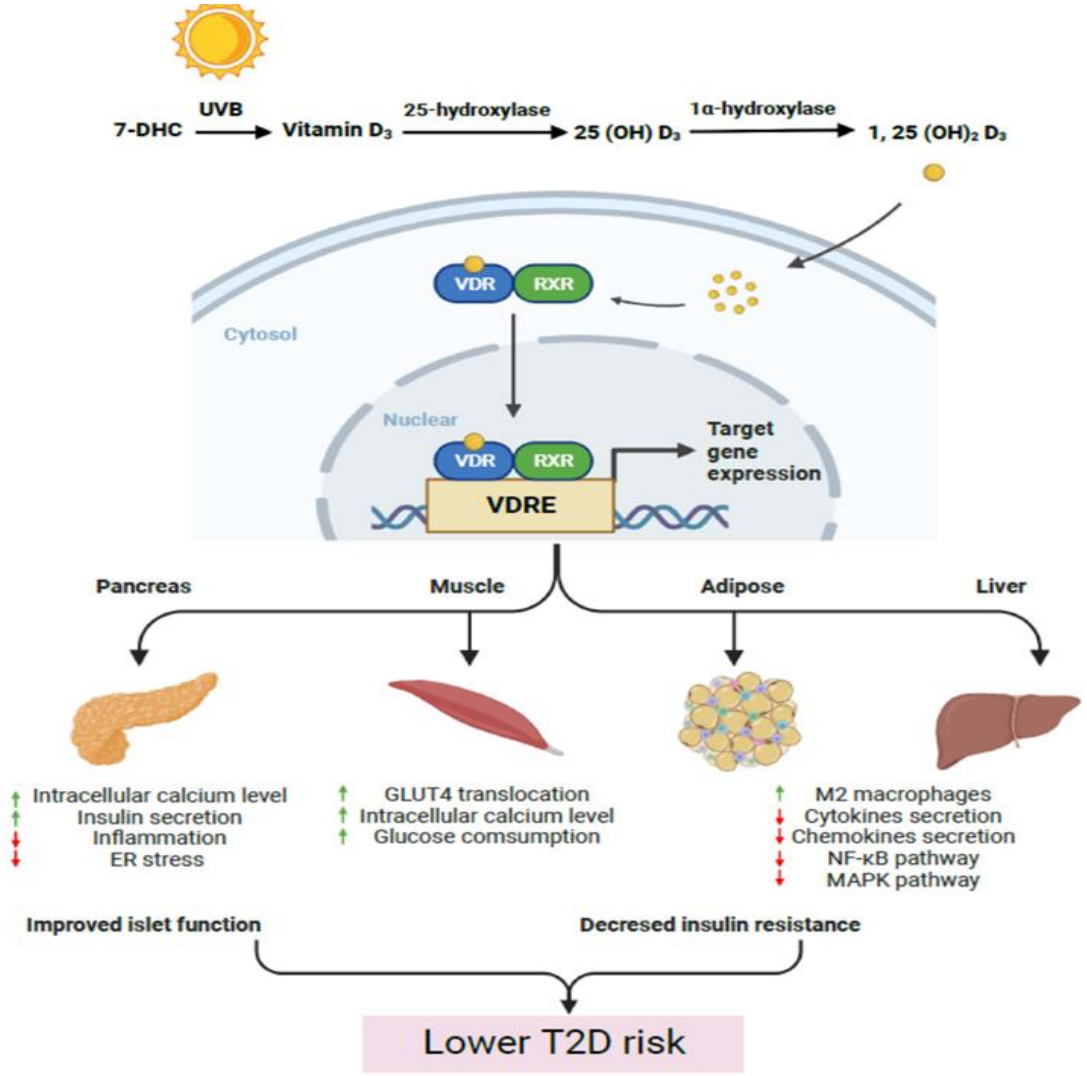


Figure (2.4): Vitamin D protects against T2DM. The active VDR/RXR heterodimer binds to VDREs to induce changes in gene expression that in combination, improve islet function and decrease insulin resistance (Wu *et al*., 2023).

Moreover, the overexpression of VDR for β cells in transgenic mice increases protection from diabetes, provides preserved β cells mass and reduces islets inflammation (Morró *et al*., 2020), in addition, vitamin D reduces both of fasting blood glucose and insulin and ameliorates each of glucose tolerance and insulin sensitivity in T2DM mice (Liu *et al*., 2023).

Moreover, vitamin D deficiency increases the risk of HOMA-IR and T2DM by inhibiting insulin synthesis and release and by lowering peripheral glucose uptake (Sung *et al*., 2012), in addition, vitamin D deficiency is associated with high levels of parathyroid hormone that caused insulin resistance and decreases insulin sensitivity (Baidya *et al*., 2024).

Many studies showed that vitamin D deficiency is prevalent in diabetic type 2 women, with a strong inverse correlation between vitamin D levels and HbA1c suggesting a possible connection between glycemic control (fasting glycemia, postprandial glycemia and HbA1c) and vitamin D metabolism (Bhat *et al*., 2021; Majeed *et al*., 2022), moreover, vitamin D plays a potential role in glycemic control and diabetes management (Al-Qahtani *et al*.,2024).

Furthermore, Al-Qahtani and his colleagues (2024) mentioned that vitamin D deficiency is associated with C-peptide levels in diabetic type 2 women, C peptide, a byproduct of insulin production serves as a valuable marker in assessing β-cells function and endogenous insulin secretion, fasting C peptide levels provide insights into the functional capacity of the pancreas and the progression of T2DM (Ludvigsson, 2016), in addition, Balla and his colleagues (2018) found that vitamin D deficiency associated with low levels of C-peptide and high levels of HbA1c in women with T2DM.

Moreover, Saeed and his colleagues (2020) observed that vitamin D supplementation was associated positively with insulin and C-peptide levels in women with T2DM, similarly, diabetic type 2 women with high intake of vitamin D have a higher C-peptide values (Cardoso-Sánchez *et al*., 2015).

Vitamin D supplementation could improve glucose tolerance, pancreatic β-cells function and insulin sensitivity (Lahbib *et al*., 2015), in addition, vitamin D supplementation significantly decreases fasting blood glucose and HbA1C levels in diabetic type 2 women (Alemam *et al*., 2022).

Moreover, a recent systematic review and meta-analysis of 46 randomized clinical trials showed that vitamin D supplementation reduced the HbA1c up to 0.2%, glycemic control ability by vitamin D intake is more intense in diabetic patients with vitamin D deficiency (Farahmand *et al*., 2023), in addition, 60% of the insulin sensitivity improvement occurred after the increase of vitamin D (Chiu *et al*., 2004).

On the other hand, each of the deficiency of vitamin D and T2DM are usually recognized as a complication and risks for thyroid diseases (Van Belle *et al*., 2013), in addition, T2DM increases the risk of thyroid dysfunction in the long term (Centeno Maxzud *et al*., 2016).

Moreover, vitamin D deficiency is associated with high levels of TSH, T3, and T4 in women attacked with diabetes type 2 alone or with subclinical hypothyroidism together (Aljabri, 2019) and similarly in women with newly diagnosed diabetic neuropathy (Salman Jasim *et al*., 2022).

Vitamin D deficiency is associated with high levels of ALT and AST in women with diabetic type 2 (Bakhuraysah *et al*., 2023), similarly, Fang and his team (2024) showed that deficiency of this vitamin associated negatively with high levels of ALT in women with diabetes type 2 who suffer from NAFLD, moreover, Seo and his colleagues (2013) observed that women with diabetic type 2 who were deficient in vitamin D had high ALP levels.

2.7 Vitamin D deficiency related with hyperprolactinemia

Hyperprolactinemia (HPL) is a condition characterized by higher-than-normal levels of serum prolactin, as a result of pituitary disorders found in both sexes with abnormal sexual and reproductive functions (Hoskova *et al*., 2022), in addition, the prevalence of HPL ranges 9-17% in women with reproductive disorders, about 3.5 times in females more than males and about 0.4% in the adult

population as general (Paepegaey *et al*., 2017), moreover, HPL is typically defined as a fasting serum prolactin level > 20 ng/mL in men and > 25 ng/mL in women (Halbreich *et al*., 2003).

Different physiological, pathological (tumor and nontumor related), and pharmacological factors are beyond the HPL occurrence , physiological factors including pregnancy, lactation, ingestion of high-protein diets, stress, sleep, physical exercise, pathological factors including PRL-secreting pituitary adenoma (prolactinoma) (Zeng *et al*., 2023;Dzialach *et al*., 2024) pharmacological factors including dopamine inhibition drugs (e.g., antipsychotics and metoclopramide), or medications that inhibit dopamine synthesis (e.g., oestrogen) (Madhusoodanan *et al*., 2010).

Moreover, HPL is common in hypothyroidism women and consist about 20-40% of these patients (Singh, 2024), the high levels of thyrotropin-releasing hormone (TRH) that stimulate the secretion of prolactin may be the cause for HPL in primary hypothyroidism individuals (Hekimsoy *et al*., 2010), in addition, patients with hypothyroidism have low of prolactin clearance and a little sensitivity of the inhibitory actions to dopamine and its agonists thereby prolactin increase and occurrence of HPL (Seri *et al*., 2003).

Hyperprolactinemia is common amongst the cirrhosis patients which their prolactin levels are less than 100 µg/L, notably that prolactin is considered as a prospective biomarker of fatty liver's in women mainly (Balakrishnan and Rajeev, 2017), also HPL is more frequent in PCOS women in spite of this frequency is remains unknown (Saei Ghare Naz *et al*., 2022).

Furthermore, HPL may drive for different detrimental hormonal and reproductive aspects including hypogonadotropic hypogonadism, irregular menstrual cycles (oligo-amenorrhea or polymenorrhea), galactorrhea, secondary

amenorrhoea, women's hirsutism, men's gynecomastia and decreases the fertility and libido in both sexes (Hu *et al*., 2018; Samperi *et al*., 2019).

Moreover, HPL is beyond the causes of cardiovascular diseases mortality (Auriemma *et al*., 2019), additionally, Krysiak and his coworkers 2023 indicate that prolactin excess (even mild-to-moderate) is associated with an increase risk of development of cardiovascular diseases and carbohydrate disorders, this risk is proportional to HPL degrees.

Hyperprolactinemia has been detected in many patients with different autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and autoimmune thyroid diseases, it is believed to plays a crucial role in the pathogenesis of these diseases due to the prolactin receptors interference with cytokine receptors, besides that, it has known that prolactin can modulates immune response (Tomio *et al*., 2008;Borba *et al*., 2019), in addition, prolactin modulates humoral and cellular immune responses, it induces the production of interleukin-1(IL-1), interleukin-6 (IL-6), interferon γ, expresses of interleukin-2(IL-2) receptors, modulates cytokine production and reduces the apoptosis of transitional B cells (Shelly *et al*., 2012).

Moreover, HPL influenced the bone metabolism, determining the density of bone minerals and increased the risk of fractures, in addition, the pathogenesis of hyperprolactinemia–induced bone loss is multifactorial, because both direct and indirect (hypogonadism) skeletal effects may be involved (Di Filippo *et al*., 2020).In addition, the effects of HPL on bone metabolism may be attributed to gonadotrophin-releasing hormone dysregulation and subsequent estrogen deficiency or by hyperprolactinemia itself (Vestergaard *et al*., 2002).

It is worth to note, that maintaining prolactin levels within the normal range might be beneficial in the prevention of metabolic syndrome (Korta *et al*., 2024).

Furthermore, many studies pointed out a relationship between HPL with metabolic syndrome, it's associated with insulin resistance and weight gain via the influence of high levels of prolactin on orexigenic-anorexigenic systems that regulate appetite-determining hyperphagia, therefore, increase of food intake and weight gain till to overt obesity (Brandebourg *et al*., 2007; Gierach *et al*., 2022).

Moreover, normal serum prolactin enhances adipogenesis, insulin sensitivity and inhibits lipolysis of adipose tissue, in addition, it plays a role at the liver's metabolic functions by increasing the insulin sensitivity and reducing fat accumulation, thereby preventing fatty's liver (Macotela *et al*., 2022), similarly, glucose and lipid storage regulated by transporters and key enzymes are influenced by prolactin action (Ben-Jonathan *et al*., 2006).

Hyperprolactinemia caused insulin resistance via impaired glucose tolerance and down-regulation of insulin receptors and/or may leads to post-receptors defects and these high prolactin levels promote the increase of insulin resistance and the reduction of insulin sensitivity (Pirchio *et al*., 2021; Gierach *et al*., 2022).

However, high physiological prolactin levels protects the individuals against T2DM due to its promotional role on the survival and proliferation of both beta-cells , insulin secretion and its enhancement of glucose movement balance (by increasing the mass of the beta-cells under some circumstances ie pregnancy) and has positive effects on both the activity of renal 25-hydroxycholecalciferol-1-hydroxylase and 1,25(OH)2D3 level (by lowering serum fibroblast growth factor 23), while, high pathological serum prolactin increases the risk of developing obesity and T2DM (De Castro *et al*., 2020;Saki *et al*., 2020; Yang *et al*., 2021).

On the other hand, vitamin D homeostasis may be reduced the circulating prolactin levels regardless with or with specific treatment, in addition, prolactin has a positive effect on the homeostasis of vitamin D which indicated that vitamin D status and lactotrope secretory function are reciprocally related (Saki *et al*.,

2020;Krysiak *et al*., 2021), moreover, hyperprolactinemic rats treated with vitamin D appeared a reduction in their prolactin levels (Sameer and Saleh,2023).

Moreover, vitamin D and calcium supplementation significantly increased the prolactin receptor expression and potentially improved the absorption of calcium in hyperprolactinemic female rats, thus the synergistic action of calcium absorption by vitamin D and prolactin suggests that the possibility of vitamin D as therapeutic drug for potential for HPL (Radojkovic *et al*., 2024).

Vitamin D and its receptors are directly involved in regulating the expression of dopaminergic-associated genes (Pertile *et al*., 2016), in addition, dopamine modification occurs via the signals of vitamin D that circuits dopamine molecules and affect supplementation of vitamin D controls directly or indirectly dopamine circuits (Trinko *et al*., 2016).

Moreover, vitamin D deficiency is highly prevalent in hyperprolactinemic women and adolescents girls beside the women with schizophrenia and HPL together, HPL caused a significant reduction of the precursors that needed for vitamin D synthesis (Krysiak *et al*., 2020;Nallani *et al*., 2022 ;Amanzholkyzy *et al*., 2023), in addition, this deficiency associated with high levels of prolactin secretion via its developmental role of macroprolactin complexes, beside that the supplementation of vitamin D reduced the elevated content of macroprolactin in premenopausal women with macroprolactinoma (Krysiak *et al*., 2015), furthermore, Keisala and his colleagues (2007) found that mutant mice that lack functional VDR showed an increase in serum prolactin levels.

2.8 Vitamin D deficiency related with inflammation and cytokines

Inflammation is an adaptive response that is triggered by noxious stimuli and conditions, such as infection and tissue injury (Majno and Joris ,2004) it's usually initiates within minutes in any host with a functional innate immune system, the inflammatory responses depend on different immune cells such as macrophages, dendritic cells, mast cells, neutrophils and lymphocytes (Akira *et al*., 2006), moreover, the duration of inflammatory responses varies between 48h-7days according to the degree damage caused by infection, in addition, these responses extend toward systemic effects through the excessive production of inflammatory cytokines which mediate the secretion of acute phase protein (i.e. C-reactive protein and coagulation factors) by the liver cells (Medzhitov, 2010).

Cytokines are soluble proteins secreted by various cells (lymphocytes, macrophages, natural killer cells, mast cells and stromal cells) they participate in the immune response and act as important mediators associated with the immune system's communication network (O'Shea and Murray, 2008).

Moreover, cytokines are classified depending on their role as pro-inflammatory or anti-inflammatory, pro-inflammatory cytokines (including different interleukins, tumor necrosis factor alpha (TNF-α) and interferons) facilitate inflammatory reactions and tend to stimulate immunocompetent cells, anti-inflammatory cytokines including (different interleukins, interleukin -1 receptor antagonist (IL-1 RA) and transforming growth factor beta (TGF-β)) inhibit the inflammation and suppress immune cells (Su *et al*., 2012).

Moreover, different studies may be pointed that vitamin D plays a role in modulating inflammatory responses (Calton *et al*., 2015) and enhances cytokines production through its impact on the differentiation of both the innate and adaptive immune cells (Medrano *et al*., 2018), in addition, its receptors and

metabolizing enzymes spreadation in various types of immune cells (Charoenngam and Holick, 2020).

Vitamin D acts as an adjustment cytokine factor to keep and maintains an anti-inflammatory environment (Azizieh *et al*., 2016) by decreasing and regulates the pro-inflammatory and anti-inflammatory cytokines respectively (Oluk *et al*., 2022).

In macrophages, vitamin D promotes the anti-inflammatory effects by increasing interleukin IL-10 production and reducing IL-1, IL-6 and TNF- α production (Ao *et al*., 2021).

Moreover, vitamin D plays a role in macrophage cytokine expression via modulation the expression of two key factors that regulating macrophage function and survival (macrophage inhibitory factor and macrophage surface-specific protein CD14), according to its impact by the calcium-dependent mechanism (Sun and Zemel,2008).

Vitamin D modulates nuclear transcription factors including nuclear factor β which plays a key role in immunomodulation (by interacting with VDRE in the promoter region of cytokine gene) and regulating the encoding of mediated inflammation cytokines (Xiaohua *et al*., 2021).

Vitamin D decreases the production of pro-inflammatory cytokines via regulates T-helper 17 (Th17) responses by promoting T helper 2 cells and suppressing T helper 1 cells, thereby limiting Th1-mediated inflammatory responses and tissue damage while enhancing Th2-mediated anti-inflammatory responses (Boonstra *et al*., 2001), in addition, vitamin D supplementation reduced Th17 cells activation providing human evidence that vitamin D can influence cells-mediated immunity (Konijeti *et al*., 2016).

Furthermore, vitamin D deficiency is associated with high levels of pro-inflammatory mediators, including IL-6, TNF-α, and CRP which increases the

development of many inflammatory diseases(Giannini *et al*., 2022;Laird *et al*., 2023), in addition, Zhou and Hyppönen (2023) demonstrated that the association between vitamin D and CRP were restricted to the deficiency range and only individuals with vitamin D deficiency have elevated serum CRP and may be the deficiency is the cause beyond, moreover, the production of pro-inflammatory cytokines decreases after vitamin binding to its receptors in monocytes, thus, vitamin D helps in reducing the concentrations of CRP and other inflammatory markers (Colin *et al*., 2010).

Moreover, several studies have examined the relationship between vitamin D supplementation and serum levels of inflammatory markers such as CRP and cytokines, some reports showed a significant positive link between IL10 and vitamin D and a significant negative association between TNF- α, interferon gamma and vitamin D suggesting that vitamin D therapy can reduce inflammation in some diseases settings (Krajewska *et al*., 2022 ; Antwi *et al*., 2024), in addition, vitamin D may decreases the inflammatory effects through its inhibition of the nuclear transcription factor κB that leads to reducing TNF-α concentrations, which might be suppressed the activity of CRP (Song *et al*., 2013).

Vitamin D deficiency associated with inflammatory biomarkers in patients suffering from metabolic syndrome such as obesity, furthermore, serum levels of IL-6, TNF-α and CRP tend towards higher levels in subjects with vitamin D deficiency (Pott-Junior *et al*., 2020 ; Khademi *et al*., 2022), in addition, vitamin D has an anti-inflammatory effects on adipocytes via modulates the expression of pro-inflammatory cytokines by regulating toll-like receptors , innate immune pattern recognition receptors (Dickie *et al*., 2010 ; Park and Han,2021).

Many studies demonstrated that vitamin D deficiency is highly prevalent in patients whom have a high level of inflammatory markers, including CRP and cytokines which their concentrations be influenced positively by vitamin D (Tiwari *et al*., 2014; Xiaohua *et al*., 2021), in addition, vitamin D protects

pancreatic beta cells from cytokine-induced apoptosis by affecting the expression and activity of the cytokines (Riachy *et al*., 2006).

Vitamin D supplementation significantly improves CRP levels in diabetic women and may be beneficial in alleviating inflammatory-associated complications (Mirzavandi *et al*., 2020), moreover, a hypothesis suggested by Giulietti and his colleagues (2007) that vitamin D reduces both inflammation and activation of the innate immune system by decreasing the levels of inflammatory factors in monocytes of patients with T2DM in compression with healthy individuals.

Chapter Three

Materials and Methods

3.1 Materials

3.1.1 Subjects

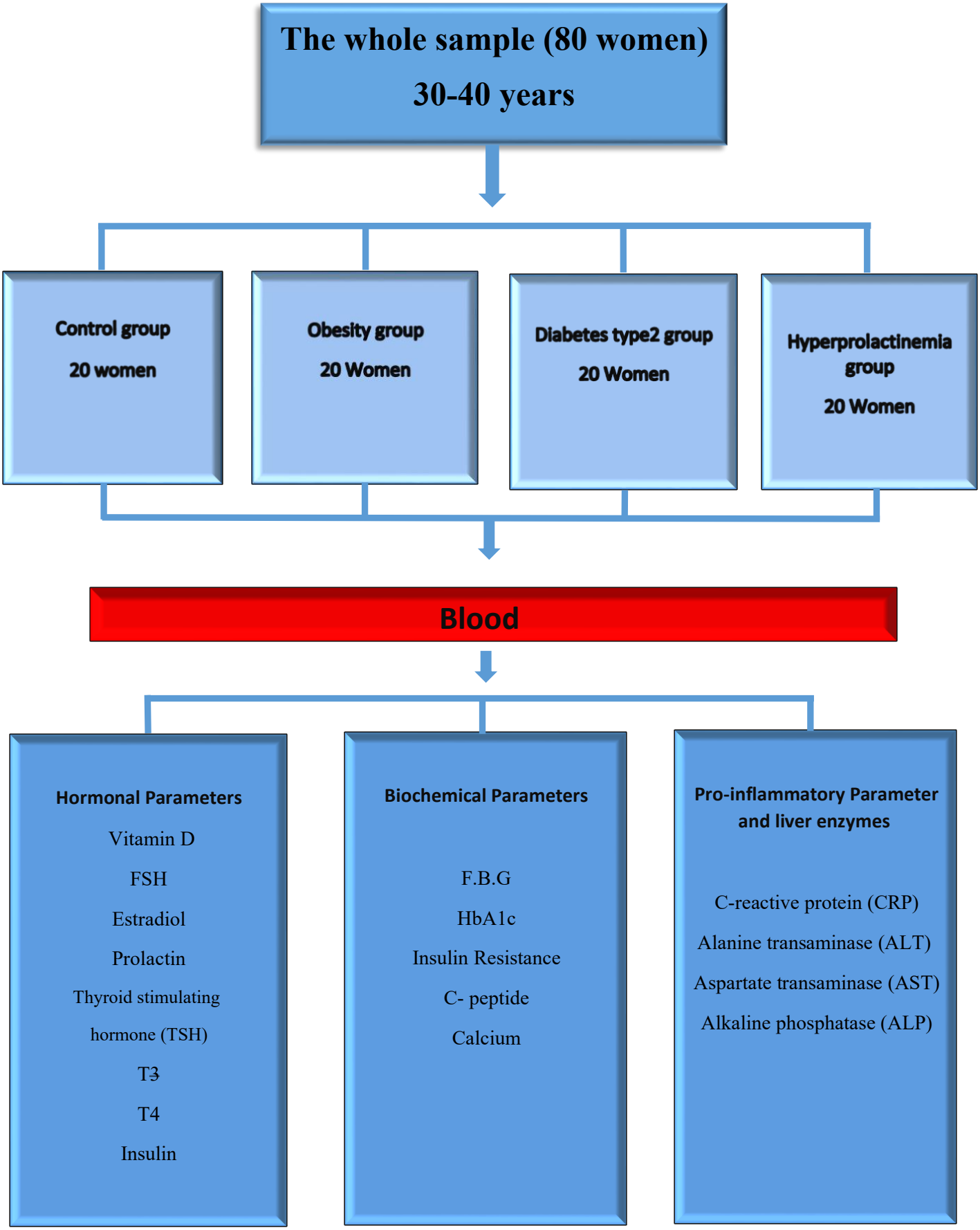
The current study was conducted in some hospitals, Maysan specialized center for endocrine diseases and diabetes and some private laboratories in Maysan province, during November 2023 to May 2025. The whole sample included 80 women aged 30 – 40 years, divided to four groups (20 women / group) as following:

- Control group (healthy women).
- Obesity group (obese women).
- Diabetes group (diabetic type 2 women).
- Hyperprolactinemia group (hyperprolactinemic women).

The participants were diagnosed based on medical evaluations by specialist physicians, the participants have been detected with obesity (BMI over 30 kg/m2), diabetic (HbA1c more than 6.5) and hyperprolactinemia (prolactin levels more than 25 ng/ml). Women with chronic diseases, tumors and those whom treated with hormonal drugs and contraceptive pills were excluded from the study.

A questionnaire has been designed to obtain the actual information about the sample individuals in Maysan province (Appendix, 1).

3.1.2 Experimental Design



3.1.3 Instruments and Equipment:

The tools and equipment used in this study and their origin are shown in Table: (3.1).

Table (3.1): The instruments and equipment used in this study

No.	Instrument	Origin
1	Alcohol	United Arab Emirates
2	Centrifuge	Japan
3	Cold box	China
4	Cotton	Turkey
5	EDTA tubes	China
6	Eppendorf tubes (1.5 ml)	Germany
7	Frozen deep freeze	Germany
8	Gel tubes	China
9	Gloves	Turkey
10	Micro pipettes (10ml, 20ml, 100ml and 200 ml)	Germany
11	Plain tubes	China
12	Staining rakes	China
13	Stature meter	China
14	Syringe	Jordin
15	Test tubes for dilution	China
16	Tips (10ml, 20ml, 100ml and 200 ml)	China
17	Vidas	France
18	Bio systems A-15	Spain
19	Mindray bs_200	China
20	Cobas e-411	Germany

3.1.4 Laboratory Kits

The laboratory kits, used in this study are show in Table (3.2).

Table (3.2): The laboratory kits used in this study. Material (Kits)

No.	Material (Kits)	Origin
1	25(OH)D	France
2	ALP	Spain
3	ALT	Spain
4	AST	Spain
5	Calcium	Spain
6	C-peptide	Germany
7	CRP	Spain
8	Estradiol	France
9	FSH	France
10	Glucose	Spain
11	HbA1c	France
12	Insulin	Germany
13	Prolactin	France
14	T3	France
15	T4	France
16	TSH	France

3.1.5 Diagnostic Kit

3.1.5.1 Vidas Automated Kits

The contents of Vidas kits for 25(OH)D, FSH, estradiol, prolactin, TSH, T3 and T4 are listed as the following:

Table (3.3): 25(OH)D vidas kits components.

Components	Specifications
25(OH)D Strips	60
25(OH)D SPRs	2 x 30
25(OH)D Control	1 x 3 ml (lyophilized)
25(OH)D Calibrator	3 x 2 ml (lyophilized)
25(OH)D Diluent	1 x 3 ml (liquid)

Table (3.4): FSH vidas kits components.

Components	Specifications
FSH Strips	60
FSH SPRs	2 x 30
FSH Control	1 x 3 ml (lyophilized)
FSH Calibrator	3 x 2 ml (lyophilized)
FSH Diluent	1 x 3 ml (liquid)

Table (3.5): Estradiol vidas kits components.

Components	Specifications
Estradiol II Strips	60
Estradiol II SPRs	2 x 30
Estradiol II Control	1 x 3 ml (liquid)
Estradiol II Calibrator	2 x 4 ml (liquid)

Table (3.6): Prolactin vidas kits components.

Components	Specifications
Prolactin Strips	60
Prolactin SPRs	2 x 30
Prolactin Control	1 x 3 ml (lyophilized)
Prolactin Calibrator	3 x 2 ml (lyophilized)
Diluent	1 x 3 ml (liquid)

Table (3.7): TSH vidas kits components.

Components	Specifications
TSH Strips	60
TSH SPRs	2 x 30
TSH Control	1 x 3 ml (lyophilized)
TSH Calibrator	1 x 2 ml (lyophilized)
Diluent	1x 3 ml (liquid)

Table (3.8): T3 vidas kits components.

Components	Specifications
T3 Strips	60
T3 SPRs	2 x 30
T3 Control	1 x 2 ml (liquid)
T3 Calibrator	1x 2 ml (liquid)

Table (3.9): T4 vidas kits components.

Components	Specifications
T4 Strips	60
T4 SPRs	2 x 30
T4 Control	1 x 3 ml (liquid)
T4 Calibrator	1x *4* ml (liquid)

3.1.5.2 Cobas Automated Kits:

- **Insulin hormone kit.**

Materials required (but not provided):

1. insulin Cal Set , for 4 x 1.0 mL.

2. Control multi marker , for 6 x 2.0 mL.

3. Control universal , for 4 x 3.0 mL.

4. Control universal , for 4 x 3.0 mL (for USA) .

5. Control multi marker , for 6 x 2.0 mL (for USA) .

6. General laboratory equipment .

7. Pro cell , 6 x 380 mL system buffer .

8. Clean cell , 6 x 380 mL measuring cell cleaning solution .

9. Elecsys Sys Wash , 1 x 500 mL wash water additive .

10. Adapter for Sys Clean .

11. Assay cup , 60 x 60 reaction cups

12. Assay tip , 30 x 120 pipette tips .

13. Clean- liner .

- **C-peptide kit.**

Materials required (but not provided) :

1. C-peptide Cal Set , for 4 x 1.0 mL.

2. Control multi marker , for 6 x 2.0 mL.

3. Control multi marker , for 6 x 2.0 mL (for USA).

4. Diluent multi Assay , 2 x 16 mL sample diluent equipment .

5. General laboratory equipment .

6. Pro cell , 6 x 380 mL x mL system buffer .

7. Clean cell , 6 x 380 mL measuring cell cleaning solution .

8. Elecsys Sys Wash , 1 x 500 mL wash water additive .

9. Adapter for Sys Clean .

10. Assay cup , 60 x 60 reaction cups

11. Assay tip , 30 x 120 pipette tips .

12. Clean- liner .

3.1.5.3 Mindray Automated Kits

1. CRP.

2. HbA1c

Table (3.10) : Mindray kit components.

No	Item	Specifications
1	reagent	2vial
2	Disposable stirrers	2×50
3	Negative control	1 ×1 ml
4	Positive control	1 ×1 ml
5	Test cads	3

3.1.5.4 Bio-System Spectrophotometer Automated Kits:

The following equipment and their components are listed:

1- Calcium kit.

Reagent: 10 x 50 mL, containing Arsenazo III (0.2 mmol/L) and imidazole - (75 mmol/L)

2- ALT kit.

• Reagent: Tris 150 mmol/L, L-alanine 750 mmol/L, lactate dehydrogenase > 1350 U/L, Ph 7.3.

• Reagent: NADH 1.3 mmol/L, 2-oxoglutarate 75 mmol/L, Sodium hydroxide 148 mmol/L, sodium azide 9.5 g/L.

Supplementary Apparatus:

Analyzer, spectrophotometer, or photometer with a cell holder thermostat that can read at 340 nm and can operate at 30 or 37 °C. 1 cm light path in the cuvettes.

3-AST kits.

• Reagent: Tris 121 mmol/L, L-aspartate 362 mmol/L, malate dehydrogenase > 460 U/L, lactate dehydrogenase > 660 U/L, Sodium hydroxide 255 mmol/L, pH 7.8.

• Reagent: NADH 1.3 mmol/L, 2-oxoglutarate 75 mmol/L, Sodium hydroxide 148 mmol/L, sodium azide 9.5 g/L.

Supplementary Apparatus:

Include an analyzer, spectrophotometer, or photometer with a cell holder that can read at 340 nm and can be thermostat at 30 or 37 °C.

4-ALP kits.

• Reagent: 0.4 mol/L of 2-amino-2-methyl-1-propanol, 1.2 mmol/L of zinc sulfate, and N-hydroxyethylethylenediaminetriacetic Mg acetate 2.5 mmol / L, pH 10.4, acid 2.5 mmol / L.

• Reagent: 60 mmol/L of 4-Nitrophenylphosphate.

Supplementary Apparatus:

Analyzer, spectrophotometer ,or photometer with cell holder a thermostat able at 25, 30, or 37 °C, and able to read at 405 nm. Cuvettes with 1 cm light path.

3.2 Methods

3.2.1 Blood Samples

Eight to ten milliliters of venous blood were collected between 9:00 and 11:00 AM, during the follicular phase (8^{th} -10^{th} day) of women's menstrual cycle, using the disposable needle, and plastic syringe for each woman. The blood was left at room temperature for (15) minutes for coagulation, centrifuged at (3000) rpm for (5) minutes, then the blood was divided into fractions into EDTA tube for HbA1c determination and serum transferred for storage (-20°C).

3.2.2 Body Mass Index (BMI)

According to WHO, (2020) BMI is calculated by dividing the weight (kg) on the square of height (m2).

3.2.3 Determination of Hormones Assay

3.2.3.1 Determination of (25(OH) D, FSH, estradiol and prolactin):

Determinate by using vidas system, with human 25(OH)D, FSH, estradiol and prolactin kits.

Fundamental principle of testing

1 -Extract the required components from the kit, and store the remaining components at a temperature range of 2-8°C.

2 - Give the components sufficient time to equilibrate 25ºC, which typically takes around 30 minutes.

3 -Test control or calibrator for each sample: use one strip (25(OH)D, FSH, estradiol and prolactin) and one SPR (25(OH)D, FSH, estradiol and prolactin). After the proper SPRs have been removed.

4 - Use the code of (25(OH)D, FSH, estradiol and prolactin) to recognized the test. The calibrator identified via S1.

5 - If necessary, label the (25(OH)D, FSH, estradiol and prolactin) Reagent Strips with the sample ID numbers.

6 - Combine the calibrator, control, and sample by vortex type mixer,

7 - The volume required for this test is 200 µl for each of the calibrator, control, and sample.

8 - Load the detector strips and SPRs for 25(OH)D, FSH, estradiol, and prolactin into their designated positions on the instrument. Verify that the color labels on the SPRs and reagent strips match the assay code.

9 - Start the assay run according to the guidelines outlined in the Vidas Operator's Manual by bioMérieux. The system will perform all assay procedures automatically.

10 - After pipetting, tightly seal the vials and adjust them to the necessary temperature.

11 - The assay will be completed in approximately 40 minutes. Once finished, remove the SPRs and detector strips from the instrument.

3.2.3.2 Determination of thyroid hormones (T3, T4 and TSH):

As described in (25(OH)D, FSH, estradiol and prolactin) hormones determination method. using Vidas system to determinate T3, T4 and TSH human equipment.

3.2.4 Determination of Biochemical Assay

3.2.4.1 Determination of insulin hormone

Cobas automated system uses to analysis insulin hormone, with human insulin kit (Weiss, 2013).

The principle

Sandwich principle. Total duration of assay: 18 minutes.

1st incubation: Insulin from 20 µL sample, a biotinylated monoclonal insulin-specific antibody, and a monoclonal insulin-specific antibody labeled with a ruthenium complex) form a sandwich complex.

2nd incubation: After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.

The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell/ProCell M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.

Results are determined via a calibration curve which is instrument specifically generated by 2-point calibration and a master curve provided via the reagent barcode or e-barcode.

Fundamental principle of testing

Bring the cooled reagents to approximately 20 °C and place on the reagent disk (20 °C) of the analyzer. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the bottles (Weiss, 2013).

Calculation of Results

The analyzer automatically calculates the analyte concentration of each sample (either in µU/mL or pmol/L).

Conversion factors:

µU/mL x 6.945 = pmol/L

pmol/L x 0.144 = µU/mL

(Weiss, 2013).

3.2.4.2 Determination of C-peptide

C-peptide was analyzed using Cobas automated system, with human C-peptide kit (Yosten and Kolar, 2015).

Sandwich principle. Total duration of assay: 18 minutes.

1st incubation: 20 µL of sample, a biotinylated monoclonal C-peptide-specific antibody, and a monoclonal C-peptide-specific antibody labeled with a ruthenium complex) react to form a sandwich complex.

2nd incubation: After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.

The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell/ProCell M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.

Results are determined via a calibration curve which is instrument specifically generated by 2-point calibration and a master curve provided via the reagent barcode or e-barcode.

Fundamental principle of testing

Bring the cooled reagents to approximately 20 °C and place on the reagent disk (20 °C) of the analyzer. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the bottles.

Calculation of Results

The analyzer automatically calculates the analyte concentration of each sample in nmol/L, ng/mL or pmol/L (selectable).

Conversion factors:

ng/mL (µg/L) x 0.33333 = nmol/L

ng/mL x 333.33 = pmol/L

nmol/L x 3.0 = ng/mL

pmol/L x 0.003 = ng/mL

3.2.4.3 Determination of Glucose Assay

Assay principle

Glucose was evaluated by using Mindray system, with human glucose kit. The serum glucose was determined by enzymatic colorimetric (GOD-PAP) method, using kit supplied by Spin react, Spain (Trinder, 1969).

Assay procedure:

Solutious	Sample	Standard	Blank
Working reagent	(lml)	(lml)	(lml)
Standard		10µL	
Sample	10µL		

Mixed and incubate for (10 min) at (37 ºC) or (20 min) at the room-temperature (15-25. ºC) reading of the absorbance A of the samples and the standard-against the blank at 505 nm. The color is stable for (30 min).

Calculations:

Glucose mg/dl= $\boldsymbol{Asample}$ /$\boldsymbol{Astandard}$× **100**

3.2.4.4 Determination of Homeostatic-Model-Assessment for Insulin-Resistance (HOMA – IR) Assay:

Is calculated by dividing:

(Fasting-insulin) (μU/mL) x (fasting-glucose) (mg/dl) ÷ 405 (Onishi *et al*., 2010).

3.2.4.5 Determination of Glycated Hemoglobin A1c (HbA1c) Assay:

HbA1c was evaluated by using Mindray system, with human HbA1c kit.

Assay principle.

1 - The glycated hemoglobin A1c kit was taken out of the fridge for 10 min.

2 - Load the detectors into their respective slots on the external device.

3 - Collect 2ml of blood using a medical syringe and transfer it to an EDTA tube. Then, gently mix the sample by inverting the tube several times.

4 - Before conducting the assay, the sample tubes were allowed to reach (25°C).

5 - Insert the sample tube into the D-10 sample rack and place it in the designated spot within the D-10 device."

6 - Patient QC ID was appearing on the screen after they have been a scanned by the barcode reader.

7 - After entering each patient ID, click the done button.

8 - To start the analysis, press the start button

9 - The steps for the device followed to start the calibration process automatically.

3.2.5 Determination of Pro-inflammatory Assay

3.2.5.1 Determination of C-reactive protein (CRP)

CRP levels are assessed using the Mindray automated analyzer with a human CRP kit (Osmand *et al*., 1977).

The Procedure

The reagent and sample allowed to reach to room temperature. The (50 µL) of the samples placed and one drop of each, positive and negative controls into the separate circles, on the slide test. The CRP-latex reagent, mixed vigorously or on the vortex mixer before used and added 1 drop (50 µL) next to the samples to be tested. The drops mixed with the stirrers, spread them over the entire-surface of the circle. Different stirrers, were used for each sample. The slide placed on a mechanical rotator at 80-100 r.p.m for 2 minutes.

Calculation of Results

The automated analyzer determined CRP levels using a prepared calibration curve. It's recommended to develop a multi-point calibration curve with a CRP multi-standard set and adjust calibration frequency according to instrument usage and assay specifics. Initial calibration should be daily.

3.2.6 Determination of Calcium Assay

3.2.6.1 Determination of calcium

Calcium was analyzed with BioSystem automated spectrophotometer, with human calcium kit (Friedman and Young, 1989).

The principle:

Calcium in the sample reacts with arsenazo III forming a coloured complex that can be measured by spectrophotometry.

Reagent preparation

Reagent is provided ready to use.

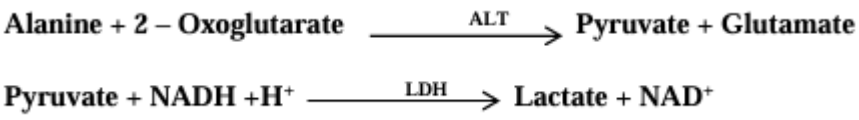
3.2.7 Determination of Liver Enzymes

3.2.7.1 Alanine transaminase (ALT) Enzyme:

ALT was evaluated by using spectrophotometer BioSystem automated, with human ALT kit (Clínica *et al*., 1987).

Fundamental principle of testing:

Alanine aminotransferase (ALT) facilitates the transfer of an amino group from alanine to 2-oxoglutarate, resulting in the formation of pyruvate and glutamate. The enzyme's catalytic activity is measured by monitoring the rate of NADH decrease at 340 nm through a coupled reaction with lactate dehydrogenase (LDH).



Preparing the reagent:

To prepare the working reagent, combine the contents of reagent B with reagent A in a 1:4 ratio (1 mL reagent B to 4 mL reagent A). Mix gently. The mixture is stable for 2 months at 2-8°C. For the pyridoxal phosphate working reagent, mix 10 mL of working reagent with 0.1 mL of reagent C (cod 11666), which is stable for 6 days at 2-8°C.

Fundamental principle of testing:

1.Allow the instrument and working reagent to reach the optimal reaction temperature.

2.Pipette the sample into a cuvette

Reaction temperature	37 ºC	30 ºC
Active Reagent Sample	0.1 MI 50 µL	0.1 Ml 100 µL

3. After mixing, insert the cuvette into the photometer and start the stopwatch.

4. Absorbance readings were recorded 1 minute after initiation and continue every minute for 3 minutes.

5.Calculate the mean absorbance difference per minute (A/min) from the differences between consecutive readings.

Calculations:

The ALT/GPT concentration in the sample is calculated using the following general formula:

ΔA / min x vt x 106 / εx1 xVs = U/L

The following formulas are derived in order to determine the catalytic concentration:

	37℃	30℃
ΔA/min	x 3333 = U/L x 55.55 =µ kat/L	x 1746 = U/L x 29.1 = µ kat/L

3.2.7.2 Aspartate Transaminase (AST) Enzyme

Using spectrophotometer BioSystem automated with human AST kit to analysis AST

(Clínica *et al*., 1987).

The principle

The enzyme AST catalyzes the transfer of an amino group from aspartate to 2-oxoglutarate, forming oxaloacetate and glutamate. Catalytic concentration is determined by measuring the rate of NADH oxidation at 340 nm used the malate dehydrogenase (MDH) coupled assay.

$$\text{Aspartate} + \text{2 – Oxoglutarate} \xrightarrow{\text{AST}} \text{Oxaloacetate} + \text{Glutamate}$$

$$\text{Oxaloacetate} + \text{NADH} + \text{H}^{+} \xrightarrow{\text{MDH}} \text{Malate} + \text{NAD}^{+}$$

Preparing the detector:

Detectors are supplied in a functional state.

Mix detector A with detector B in a 4:1 ratio (4 mL reagent A to 1 mL reagent B) and store at 2-8°C for up to 1 month. To prepare the pyridoxal phosphate reagent, combine 10 mL of working reagent with 0.1 mL of reagent C (cod 11666), stable for 6 days at 2-8°C .

The technique

1.Bring the working reagent and instrument to the temperature required for this interaction.

2.Transfer the sample to a cuvette using a pipette.

Reaction temperature	**37 ºC**	**30 ºC**
Active Reagent Sample	1.0 mL 50 µL	1.0 Ml 100 µL

3. Following combining, put the cuvette in the photometer and simultaneously start.

4. Record the first reading after (1 minute), then take subsequent readings every minute for the next 3 minutes.

5. Compute the change in absorbance (ΔA/min) from the absorbance readings taken at 1-minute intervals.

Calculations:

present in the sample:

ΔA /min x vt x 106 /εx1 xVs = U/L

Given the molar absorbance (ε) of NADH at 340 nm is 6300, the light path (l) is 1 cm, the total reaction volume (Vt) is 1.05 mL at 37°C and 1.1 mL at 30°C, and the sample volume (Vs) is 0.05 mL at 37°C and 0.1 mL at 30°C. Additionally, 1 U/L is equivalent to 0.0166 µkat/L. The following formulas can be derived to calculate the catalytic concentration:

ΔA/min	**37℃**	**30℃**
	x 3333 = U/L x 55.55 =µ kat/L	x 1746 = U/L x 29.1 = µ kat/L

3.2.7.3 Alkaline phosphatase (ALP) Enzyme

Using spectrophotometer BioSystem automated with human ALP kit to analysis (Rosalki *et al*., 1993).

The principle:

ALP facilitates the phosphate group transfer from 4-nitrophenylphosphate to AMP in alkaline conditions, producing 4-nitrophenol. The catalytic concentration is determined by measuring the rate of 4-nitrophenol formation at 405 nm.

Preparing the Reagent:

Active reagent:

Combine reagent A with reagent B according to the specified codes: For Cod: 11593 and 11592, mix one bottle of detector A with one vial of detector B. For Cod. 11598, add 25 mL of reagent B to a bottle of reagent A. In both cases, use a 4:1 ratio (4 mL reagent A to 1 mL reagent B) for additional preparations, stable for 2 months at 2-8°C.

The procedure:

1. Ensure the working reagent, pipette, and cuvette are at the same temperature as the reaction conditions.

The Sample of working Reagent	1.0 mL 20 µL

3. Mix the contents and insert the cuvette into the photometer.

4. Record initial absorbance and at 1-minute intervals thereafter for 3 minutes.

5.Determine the variation between successive absorbance readings and calculate the high absorbance change (ΔA/min).

Calculations:

The formula is used to found the levels of ALP in the serum:

ΔA /min x vt x 106 /εx1 xVs = U / L

To determine the catalytic concentration, the following formulas are derived from the data: molar absorbance (ε) of 4-nitrophenol at 405 nm = 18,450, light path (l) = 1 cm, total reaction volume (Vt) = 1.02 mL, sample volume (Vs) = 0.02 mL, and 1 U/L is equivalent to 0.0166 µkat/L.

ΔA / min	x 2764 = U / L
	x 46.08 = µ kat / L

3.3. Statistical Analysis

Statistical analysis was performed by IBM (SPSS) statistics, version 23 (IBM Co., Armonk., NY., USA). The statistical analysis was performed by the one way-Analysis-Of-Variance (ANOVA), followed by (Duncan's) a new multiple range test (DMRT) at a ($p \leq 0.05$) and ($p \leq 0.01$) significant level (Steel *et al*., 1997).

Chapter Four

Results

4.1 Hormonal Parameters

4.1.1 Vitamin D

Results showed that vitamin D levels decreased significantly ($p \leq 0.01$) for obesity (9.52 ±1.77ng/ml), diabetes (9.67 ±1.80 ng/ml) and hyperprolactinemia (9.34 ±1.70 ng/ml) groups in comparison with the control (35.85 ±4.54 ng/ml) (figure 4.1, table 4.1).

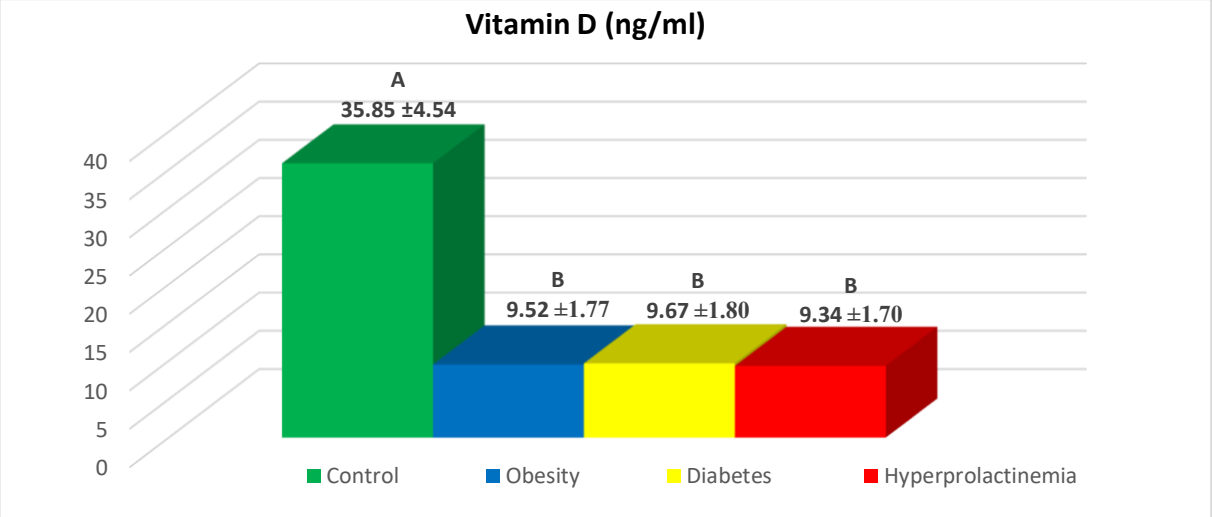


Figure (4.1): Changes of vitamin D levels during different study's groups.

*Values are expressed as mean ± SD.

*Means followed by different capital letters are significantly different between groups at $p \leq 0.01$.

*Means followed by the same capital letters are not significantly different.

4.1.2 Follicle-stimulating hormone (FSH)

Results showed that FSH levels elevated significantly ($p \leq 0.01$) for obesity (6.51 ±0.60 mlu/ml), diabetes (7.08 ±0.46 mlu/ml) groups and not significantly for hyperprolactinemia (5.52 ±0.78 mlu/ml) group in comparison with control (5.48 ±0.50 mlu/ml).

Results showed that FSH levels elevated significantly ($p \leq 0.01$) for diabetes group in comparison with obesity and hyperprolactinemia groups (figure 4.2, table 4.1).

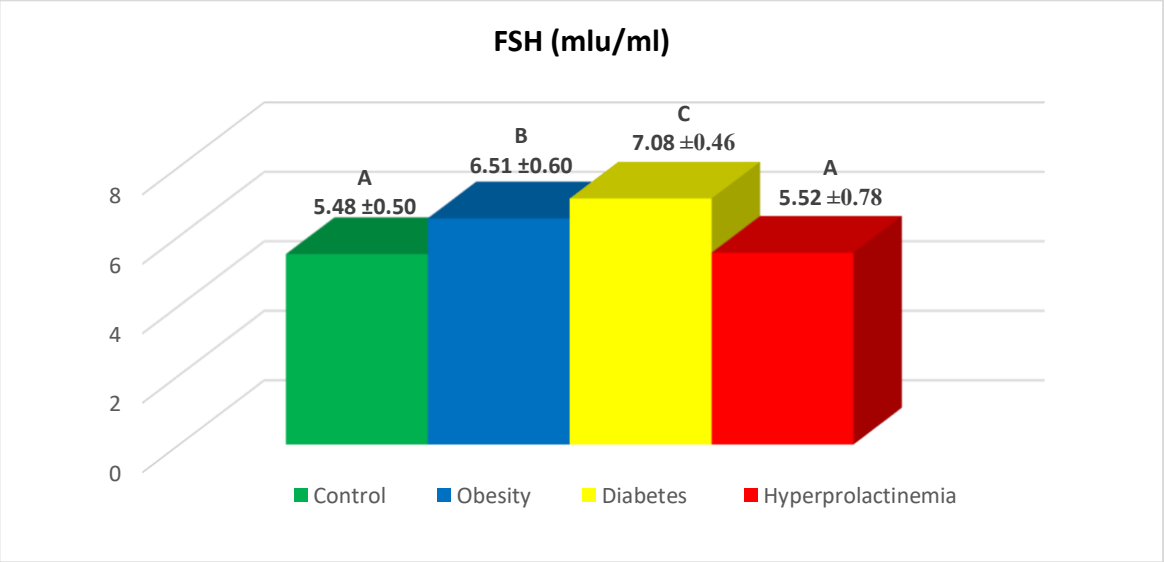


Figure (4.2): Changes of FSH levels of different study's groups.

*Values are expressed as mean ± SD.

*Means followed by different capital letters are significantly different between groups at $p \leq 0.01$.

*Means followed by the same capital letters are not significantly different.

4.1.3 Estradiol

Results showed that estradiol levels elevated significantly ($p \leq 0.01$) for obesity (89.55 ±5.89 pg/ml), diabetes (71.40±9.66 pg/ml) and hyperprolactinemia (88.95 ±8.22 pg/ml) groups in comparison with control (59.60 ±5.82 pg/ml).

Results showed that estradiol levels elevated significantly ($p \leq 0.01$) for obesity group in comparison with diabetes group and not significantly with hyperprolactinemia group (figure 4.3, table 4.1).

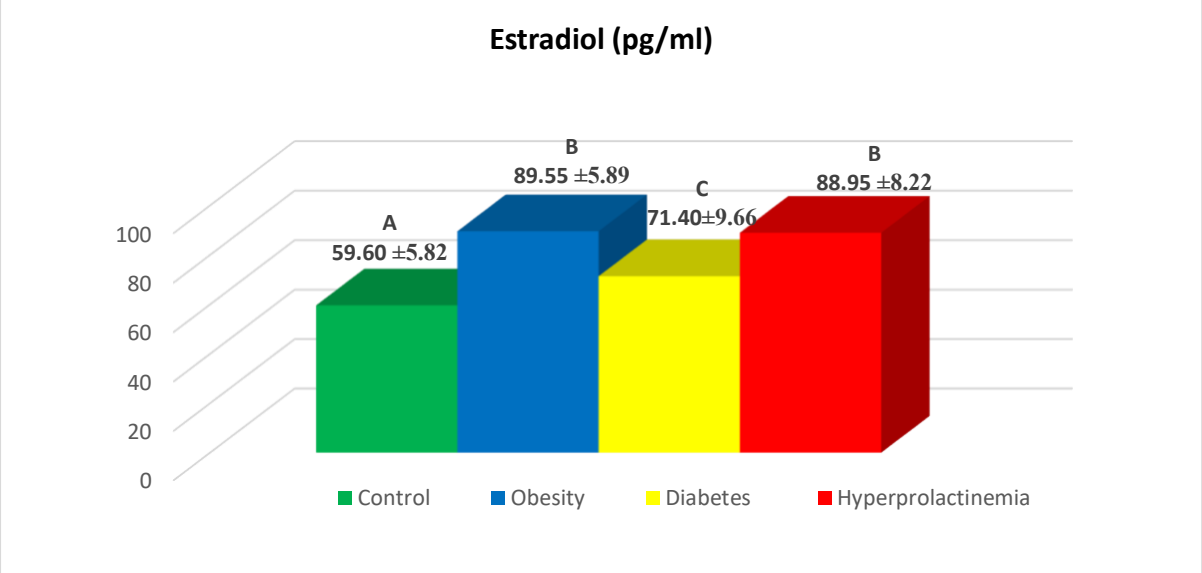


Figure (4.3): Changes of estradiol levels of different study's groups.

*Values are expressed as mean ± SD.

*Means followed by different capital letters are significantly different between groups at $p \leq 0.01$.

4.1.4 Prolactin

Results showed that prolactin levels elevated significantly ($p \leq 0.01$) for hyperprolactinemia group (49.31 ±4.32 ng/ml) in comparison with obesity (18.34±1.53 ng/ml), diabetes (16.58 ±1.28 ng/ml) and control groups (14.75 ±1.21 ng/ml).

Results showed that prolactin levels elevated significantly ($p \leq 0.05$) for obesity group in comparison with diabetes and control groups.

Results showed that prolactin levels elevated significantly ($p \leq 0.05$) for diabetes group in comparison with control (figure 4.4, table 4.1)

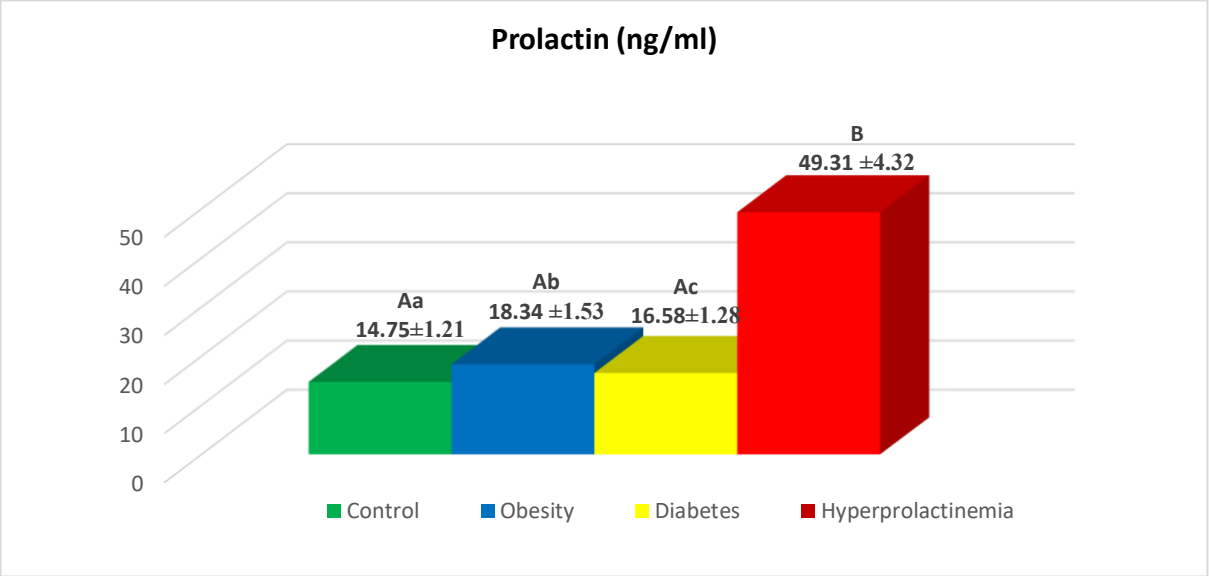


Figure (4.4): Changes of prolactin levels of different study's groups.

*Values are expressed as mean ± SD.

*Means followed by different capital letters are significantly different between groups at $p \leq 0.01$.

*Means followed by the same capital letters are not significantly different.

*Means followed by different small letters are significantly different between groups at $p \leq 0.05$.

*Means followed by the same small letters are not significantly different.

4.1.5 Thyroid-stimulating hormone (TSH)

Results showed that TSH levels elevated significantly ($p \leq 0.01$) for obesity (2.16±0.51 µUI/ml), diabetes (1.99±0.29 µUI/ml) and hyperprolactinemia groups (2.05±0.17 µUI/ml) in comparison with control (1.67±0.18 µUI/ml).

Results showed that TSH levels elevated not significantly for obesity group in comparison with diabetes and hyperprolactinemia groups.

Results showed that TSH levels decreased not significantly for diabetes group in comparison with obesity and hyperprolactinemia groups (figure 4.5, table 4.1).

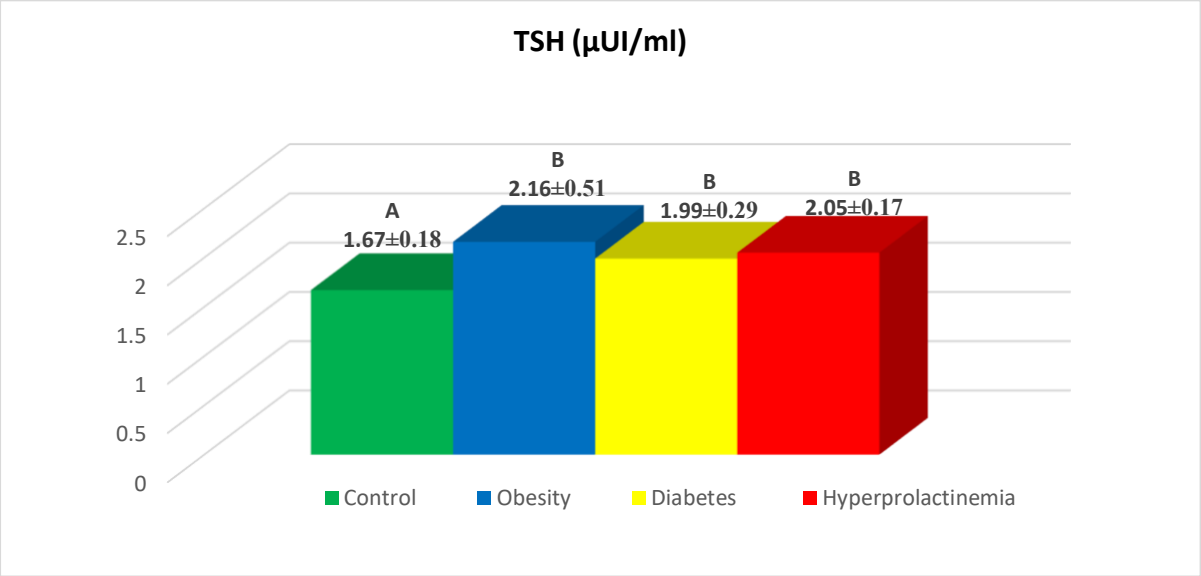


Figure (4.5): Changes of TSH levels of different study's groups.

*Values are expressed as mean ± SD.

*Means followed by different capital letters are significantly different between groups at $p \leq 0.01$.

*Means followed by the same capital letters are not significantly different.

4.1.6 Triiodothyronine (T3)

Results showed that T3 levels elevated not significantly for obesity group (1.60 ±0.206 ng/dl), diabetes (1.63 ±0.208 ng/dl) and hyperprolactinemia groups (1.62±0.111 ng/dl) in comparison with control (1.54 ±0.119 ng/dl).

Results showed that T3 levels elevated not significantly for diabetes group in comparison with obesity and hyperprolactinemia groups (figure 4.6, table 4.1).

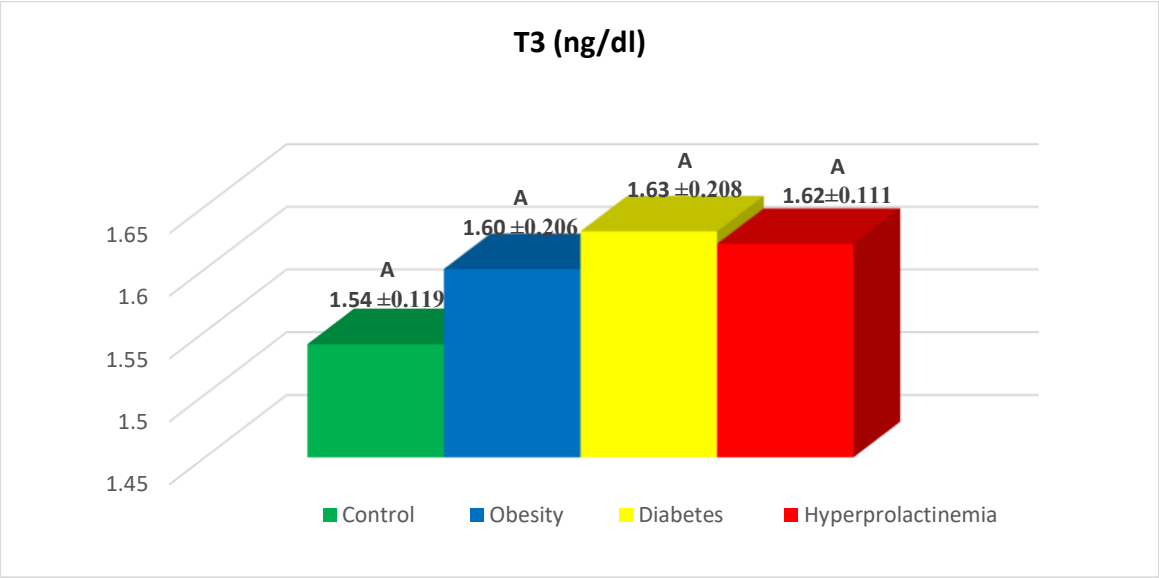


Figure (4.6): Changes of T3 levels of different study's groups.

*Values are expressed as mean ± SD.

*Means followed by the same capital letters are not significantly different.

4.1.7 Thyroxine (T4)

Results showed that T4 levels elevated significantly ($p \leq 0.01$) for obesity (89.85±6.22 ng/dl) group in comparison with diabetes (85.05±3.84 ng/dl) and control (82.7±4.79 ng/dl) groups and not significantly in comparison with hyperprolactinemia group (89.45±4.43 ng/dl).

Results showed that T4 levels elevated significantly ($p \leq 0.01$) for hyperprolactinemia group in comparison with control and significantly ($p \leq 0.05$) in comparison with diabetes groups (figure 4.7, table 4.1).

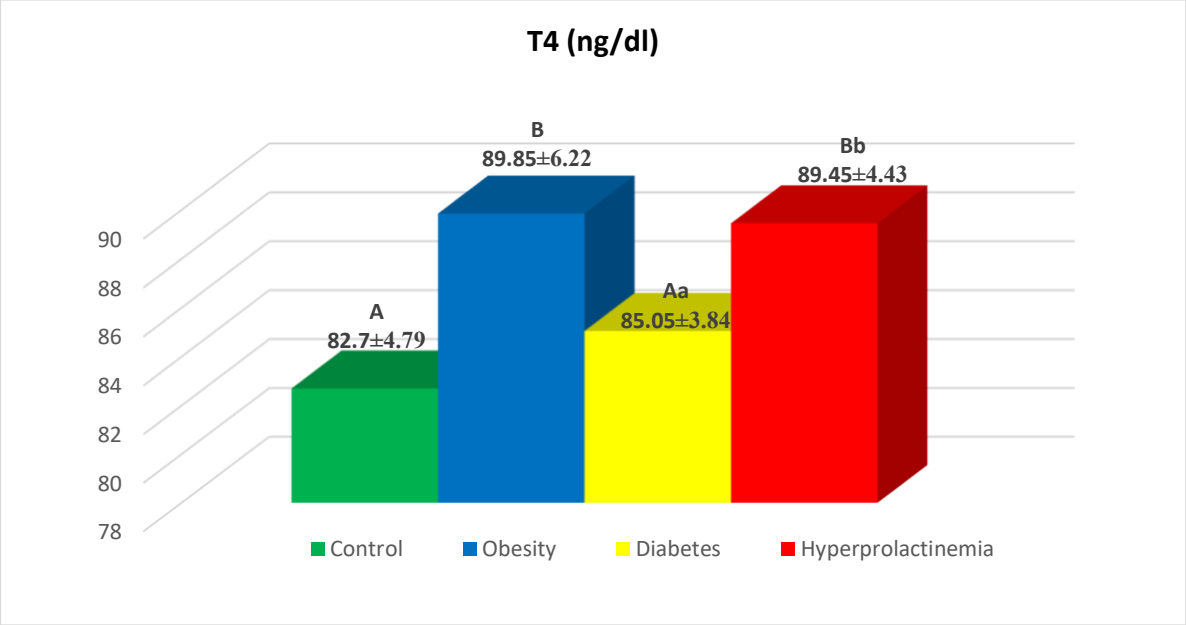


Figure (4.7): Changes of T4 levels of different study's groups.

*Values are expressed as mean ± SD.

*Means followed by different capital letters are significantly different between groups at $p \leq 0.01$.

*Means followed by the same capital letters are not significantly different.

*Means followed by different small letters are significantly different between groups at $p \leq 0.05$.

4.1.8 Insulin

Results showed that insulin levels elevated significantly ($p \leq 0.01$) for obesity (48.15±6.74 µU/ml), hyperprolactinemia (19.61±2.04 µU/ml) groups and not significantly for diabetes (15.75±1.25 µU/ml) group in comparison with control (13.98±2.38 µU/ml).

Results showed that insulin levels elevated significantly ($p \leq 0.01$) for obesity group in comparison with diabetes and hyperprolactinemia groups (figure 4.8, table 4.1).

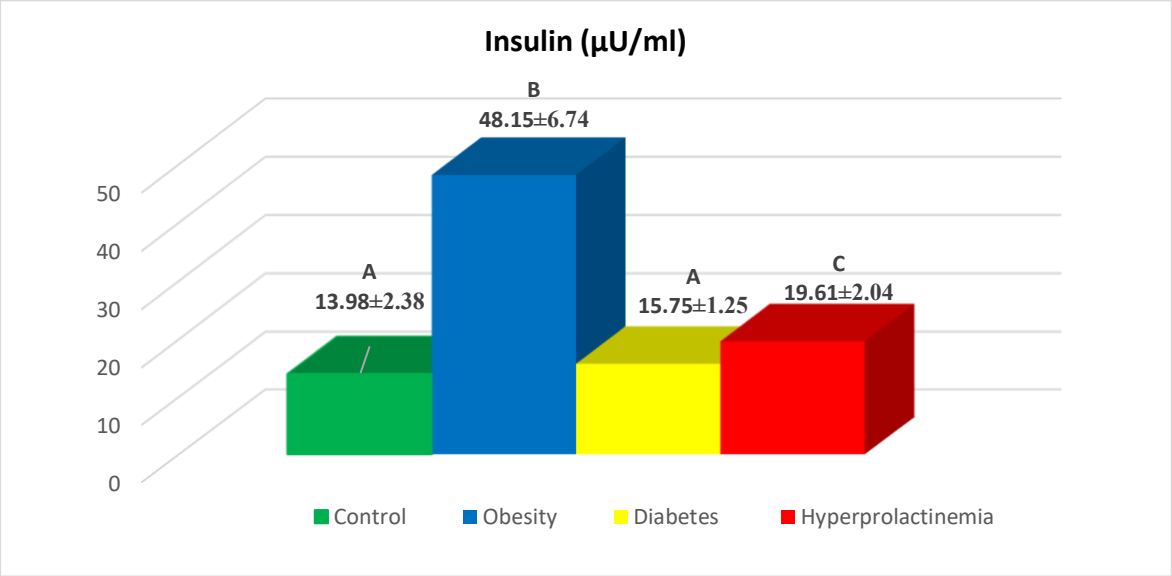


Figure (4-8): Changes of insulin levels of different study's groups.

*Values are expressed as mean ± SD.

*Means followed by different capital letters are significantly different between groups at $p \leq 0.01$.

*Means followed by the same capital letters are not significantly different.

Table (4.1): Vitamin D and hormonal changes during different study groups.

Parameters	Control	Obesity	Diabetes	Hyperprolactinemia
Vitamin D ng/ml	35.85 ± 4.54^{A}	9.52 ± 1.77^{B}	9.67 ± 1.80^{B}	9.34 ± 1.70^{B}
FSH mlU/ml	5.48 ± 0.50^{A}	6.51 ± 0.60^{B}	7.08 ± 0.46^{C}	5.52 ± 0.78^{A}
Estradiol pg/ml	59.60 ± 5.82^{A}	89.55 ± 5.89^{B}	71.40 ± 9.66^{C}	88.95 ± 8.22^{B}
Prolactin ng/ml	14.75 ± 1.21^{Aa}	18.34 ± 1.53^{Ab}	16.58 ± 1.28^{Ac}	49.31 ± 4.32^{C}
TSH µUl/ml	1.67 ± 0.18^{A}	2.16 ± 0.51^{B}	1.99 ± 0.29^{B}	2.05 ± 0.17^{B}
T3 ng/dl	1.54 ± 0.119^{A}	1.60 ± 0.206^{A}	1.63 ± 0.208^{A}	1.62 ± 0.111^{A}
T4 ng/dl	82.7 ± 4.79^{A}	89.85 ± 6.22^{B}	85.05 ± 3.84^{Aa}	89.45 ± 4.43^{Bb}
Insulin µU/ml	13.98 ± 2.38^{A}	48.15 ± 6.74^{B}	15.75 ± 1.25^{A}	19.61 ± 2.04^{C}

*Values are expressed as mean ± SD.

*Means followed by different capital letters are significantly different between groups at $p \leq 0.01$.

*Means followed by the same capital letters are not significantly different.

*Means followed by different small letters are significantly different between groups at $p \leq 0.05$.

*Means followed by the same small letters are not significantly different.

4.2 Biochemical Parameters

4.2.1 Fasting blood glucose (F.B.G)

Results showed that F.B.G levels elevated significantly ($p \leq 0.01$) for diabetes (347.45 ±42.51 mg/dl) group in comparison with obesity (103.9 ±6.81 mg/dl), hyperprolactinemia (97.1 ±6.62 mg/dl) and control (95.1 ±8.26 mg/dl) groups.

Results showed that F.B.G levels elevated not significantly for obesity and hyperprolactinemia groups in comparison with control (figure 4.9, table 4.2).

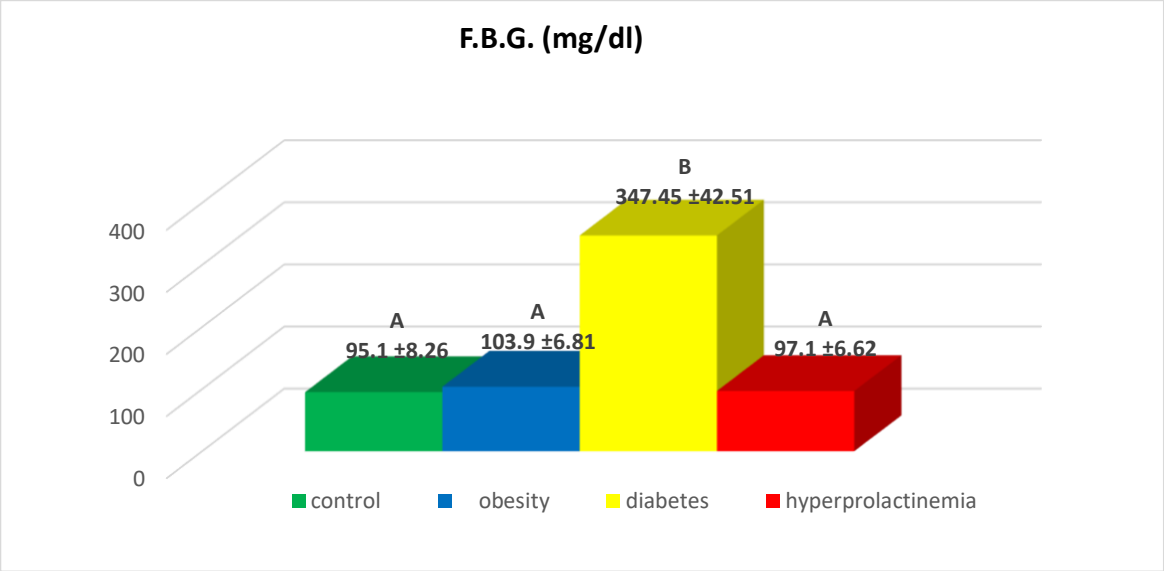


Figure (4-9): Changes of F.B.G levels of different study's groups.

*Values are expressed as mean ± SD.

*Means followed by different capital letters are significantly different between groups at $p \leq 0.01$.

*Means followed by the same capital letters are not significantly different.

4.2.2 Glycated Hemoglobin A1c (HbA1c)

Results showed that HbA1c levels elevated significantly ($p \leq 0.01$) for diabetes (8.6±0.77) group in comparison with obesity (5.3±0.37), hyperprolactinemia (5±0.27) and control (4.9±0.37) groups.

Results showed that HbA1c levels elevated not significantly for obesity group in comparison with hyperprolactinemia and control groups.

Results showed that HbA1c elevated not significantly for hyperprolactinemia groups in comparison with control (figure 4.10, table 4.2).

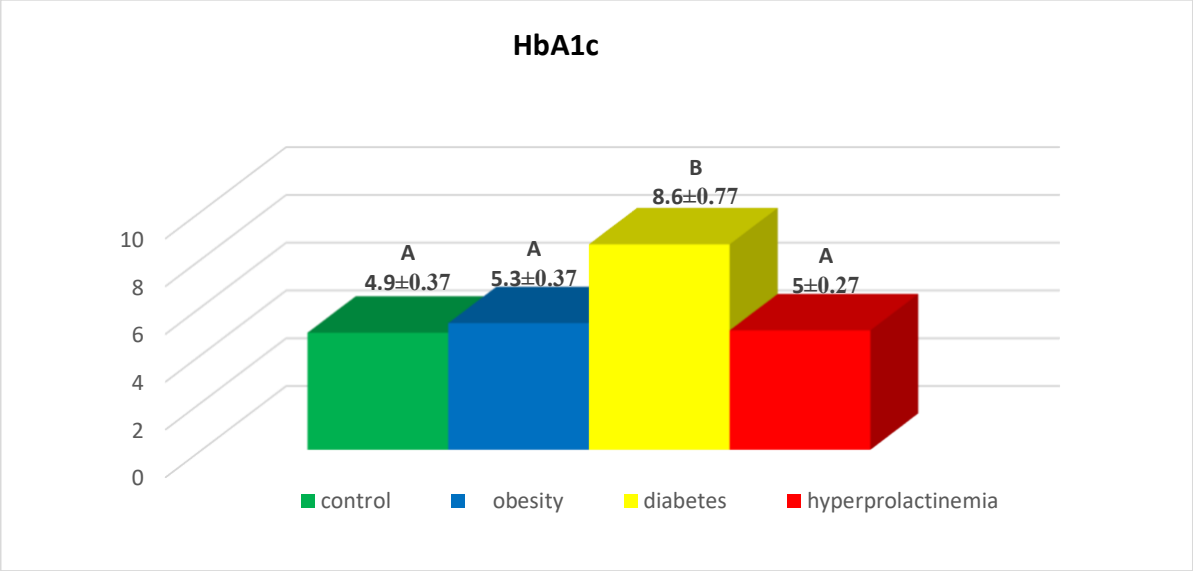


Figure (4.10): Changes of HbA1c levels of different groups.

*Values are expressed as mean ± SD.

*Means followed by different capital letters are significantly different between groups at $p \leq 0.01$.

*Means followed by the same capital letters are not significantly different.

4.2.3 Insulin Resistance

Results showed that insulin resistance levels elevated significantly ($p \leq 0.01$) for diabetes (13.55±2.25) and obesity (12.36±1.98) groups in comparison with hyperprolactinemia (4.49±0.46) and control (3.27±0.59) groups.

Results showed that insulin resistance levels elevated significantly ($p \leq 0.05$) for diabetes group in comparison with obesity group.

Results showed that insulin resistance levels elevated significantly ($p \leq 0.05$) for hyperprolactinemia group in comparison control (figure 4.11, table 4.2).

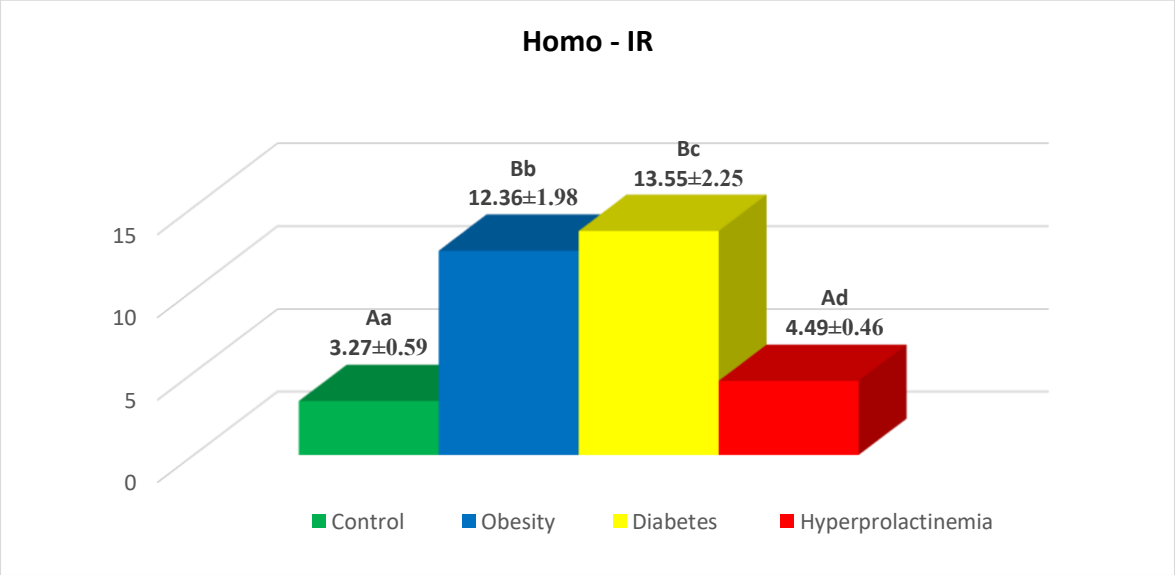


Figure (4.11): Changes of insulin resistance levels of different study's groups.

*Values are expressed as mean ± SD.

*Means followed by different capital letters are significantly different between groups at $p \leq 0.01$.

*Means followed by the same capital letters are not significantly different

*Means followed by different small letters are significantly different between groups at $p \leq 0.05$.

*Means followed by the same small letters are not significantly different.

4.2.4 C- peptide

Results showed that C- peptide levels elevated significantly ($p \leq 0.01$) for obesity (5.75 ±0.65 ng/ml) and hyperprolactinemia (4.3 ±0.58 ng/ml) groups in comparison with diabetes (3.05 ±0.54 ng/ml) and control (3.005 ±0.70 ng/ml) groups.

Results showed that C- peptide levels elevated significantly ($p \leq 0.01$) for obesity group in comparison with diabetes and hyperprolactinemia groups (figure 4.12, table 4.2).

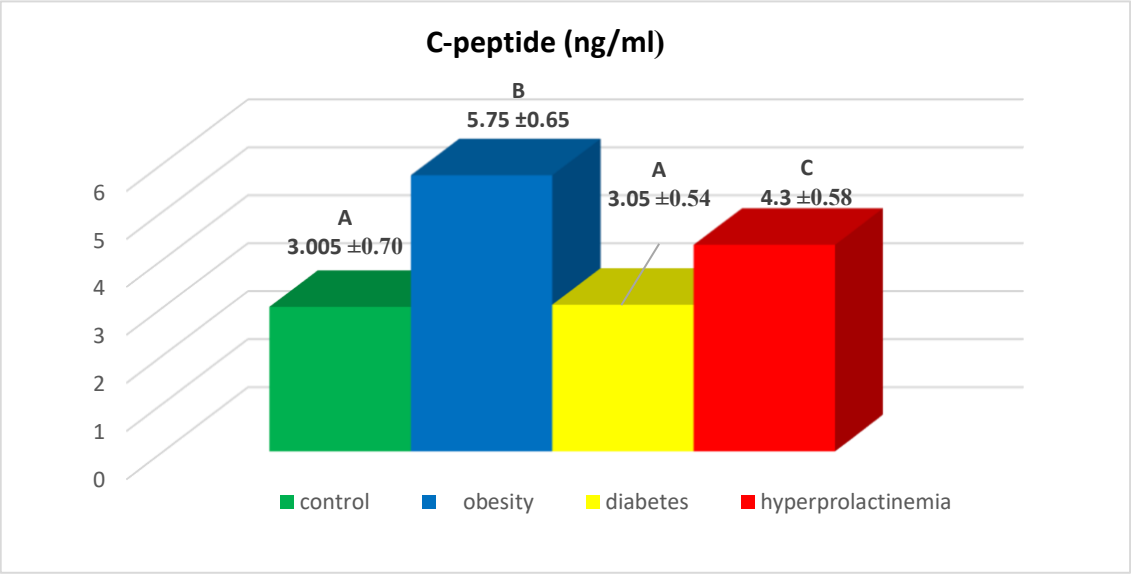


Figure (4-12): Changes of C-peptide levels of different study's groups.

*Values are expressed as mean ± SD.

*Means followed by different capital letters are significantly different between groups at $p \leq 0.01$.

*Means followed by the same capital letters are not significantly different.

4.2.5 Calcium

Results showed that calcium levels decreased not significantly for obesity (9.01±0.11 ng/ml), diabetes (9.08±0.24 ng/ml) and hyperprolactinemia (9.05±0.18 ng/ml) groups in comparison with control (9.25±0.37 ng/ml) (figure 4.13, table 4.2).

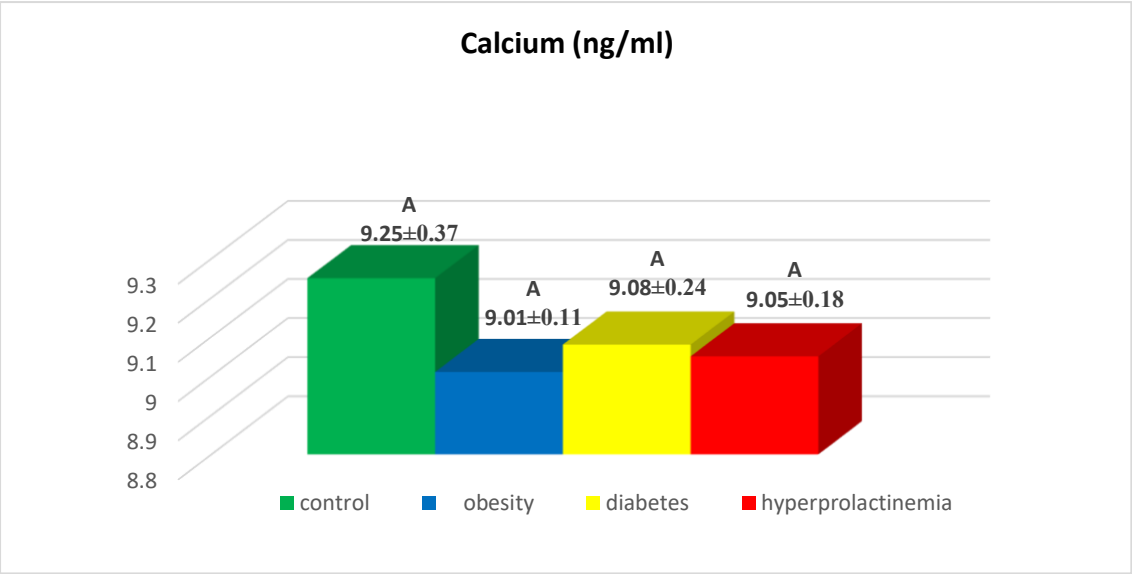


Figure (4.13): Changes of calcium levels of different study's groups.

*Values are expressed as mean ± SD.

*Means followed by the same capital letters are not significantly different.

Table (4.2): Glucose metabolic changes and calcium concentrations during different study groups.

Parameters	Control	Obesity	Diabetes	Hyperprolactinemia
F.B.G. mg/dl	95.1 ± 8.26^{A}	103.9 ± 6.81^{A}	347.45 ± 42.51^{B}	97.1 ± 6.62^{A}
HbA1c	4.9 ± 0.37^{A}	5.3 ± 0.37^{A}	8.6 ± 0.77^{B}	5 ± 0.27^{A}
Insulin resistance	3.27 ± 0.59^{Aa}	12.36 ± 1.98^{Bb}	13.55 ± 2.25^{Bc}	4.49 ± 0.46^{Ad}
C-peptide ng/ml	3.005 ± 0.70^{A}	5.75 ± 0.65^{B}	3.05 ± 0.54^{A}	4.3 ± 0.58^{C}
Calcium ng/ml	9.25 ± 0.37^{A}	9.01 ± 0.11^{A}	9.08 ± 0.24^{A}	9.05 ± 0.18^{A}

*Values are expressed as mean ± SD.

*Means followed by different capital letters are significantly different between groups at $p \leq 0.01$.

*Means followed by the same capital letters are not significantly different.

*Means followed by different small letters are significantly different between groups at $p \leq 0.05$.

*Means followed by the same small letters are not significantly different.

4.3 C-reactive protein and Liver Enzymes

4.3.1 C-reactive protein (CRP)

Results showed that CRP levels elevated significantly ($p \leq 0.01$) for obesity (6.65±0.94 mg/dl), diabetes (4.56±0.75 mg/dl) and hyperprolactinemia (3.54±0.56 mg/dl) groups in comparison with control (1.50±0.31 mg/dl) .

Results showed that CRP levels elevated significantly ($p \leq 0.01$) for obesity group in comparison with diabetes and hyperprolactinemia groups (figure 4.14, table 4.3).

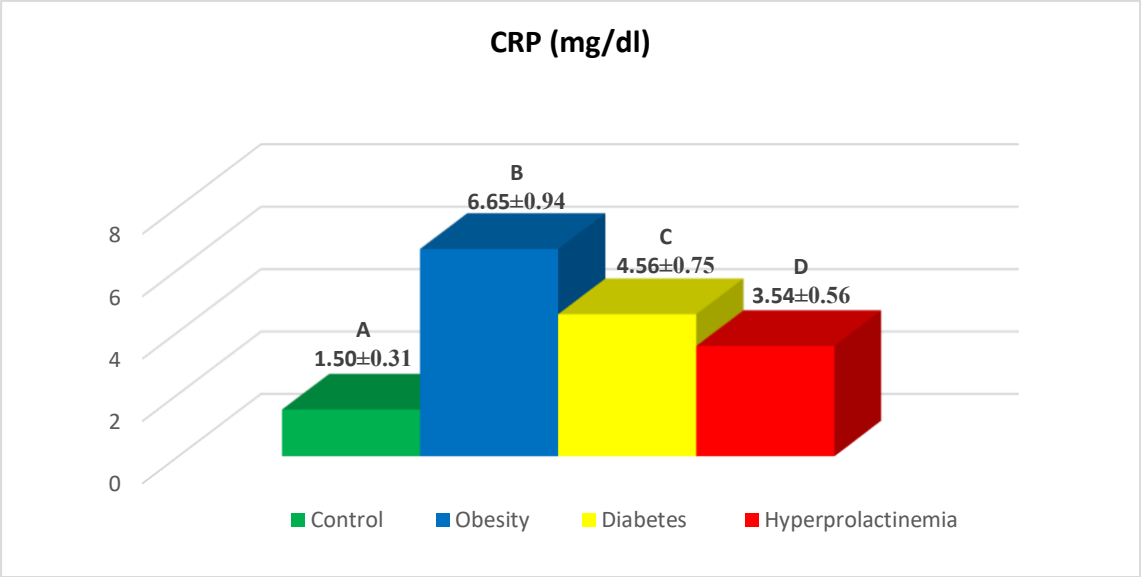


Figure (4.14): Changes of CRP levels of different study's groups.

*Values are expressed as mean ± SD.

*Means followed by different capital letters are significantly different between groups at $p \leq 0.01$.

4.3.2 Alanine transaminase (ALT)

Results showed that ALT levels elevated significantly ($p \leq 0.01$) for diabetes (20.95±2.24 U/L), obesity (16.75±2.04 U/L) and hyperprolactinemia (15.45±1.11 U/L) groups in comparison with control (12±1.44 U/L).

Results showed that ALT levels elevated significantly ($p \leq 0.01$) for obesity group in comparison with control and significantly ($p \leq 0.05$) in comparison with hyperprolactinemia groups (figure 4.15, table 4.3).

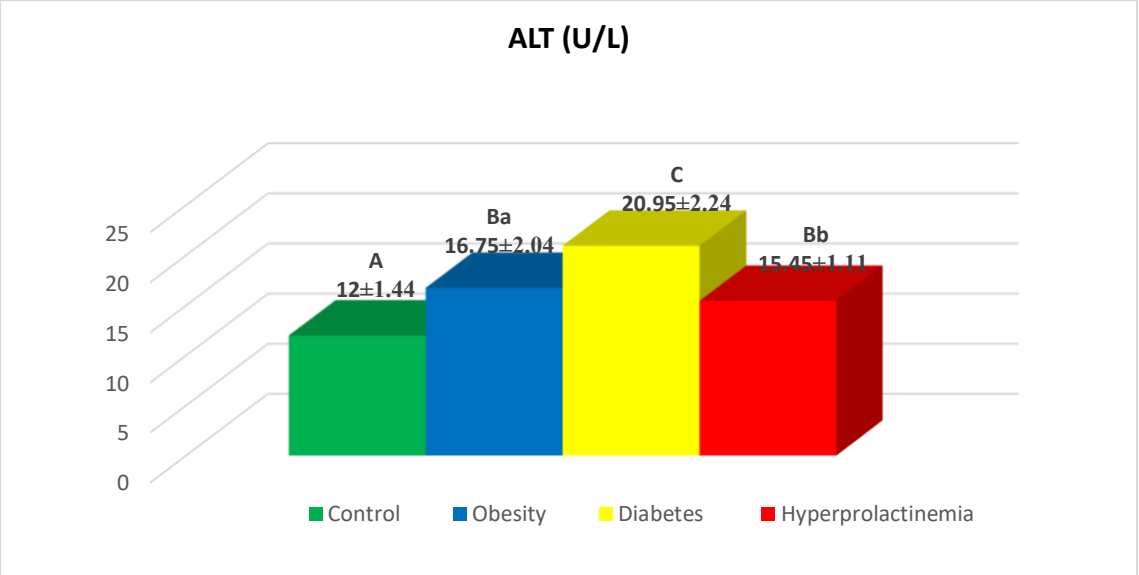


Figure (4.15): Changes of ALT enzyme levels of different study's groups.

*Values are expressed as mean ± SD.

*Means followed by different capital letters are significantly different between groups at $p \leq 0.01$.

*Means followed by the same capital letters are not significantly different.

*Means followed by different small letters are significantly different between groups at $p \leq 0.05$.

4.3.3 Aspartate transaminase (AST)

Results showed that AST levels elevated significantly ($p \leq 0.01$) for hyperprolactinemia (18.5±1.51 U/L) group in comparison with obesity (16.10±2.40 U/L), diabetes (15.65±1.49 U/L) and control (15.05±1.93 U/L) groups.

Results showed that AST levels elevated not significantly for obesity group in comparison with diabetes and control groups (figure 4.16, table 4.3).

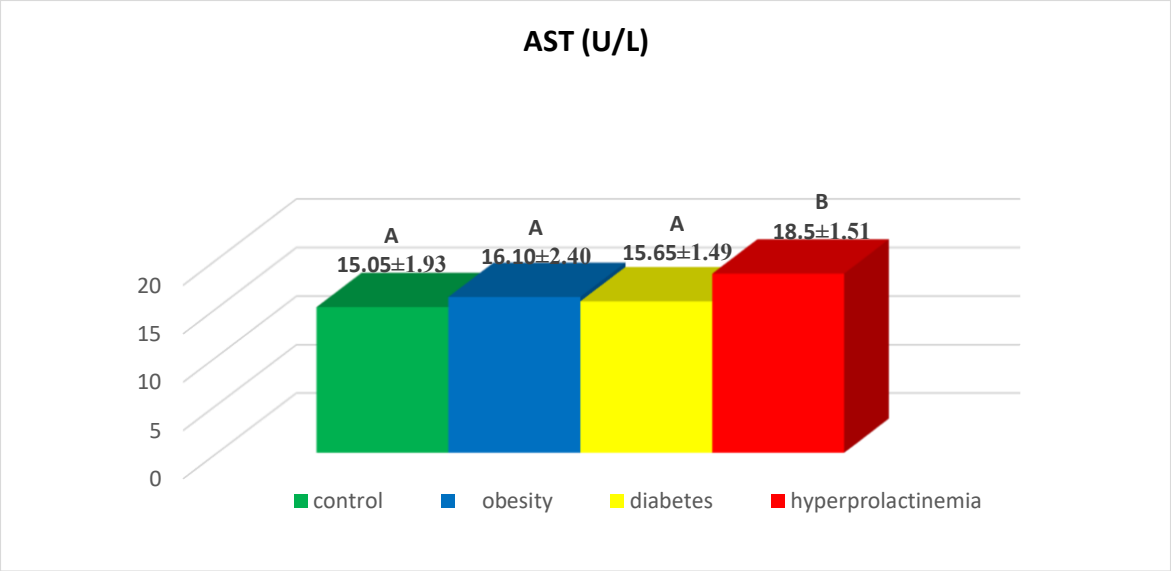


Figure (4.16): Changes of AST enzyme levels of different study's groups.

*Values are expressed as mean ± SD.

*Means followed by different capital letters are significantly different between groups at $p \leq 0.01$.

*Means followed by the same capital letters are not significantly different.

4.3.4 Alkaline phosphatase (ALP)

Results showed that ALP levels elevated significantly ($p \leq 0.01$) for diabetes (129.9±9.00U\L) group in comparison with obesity (88±3.34 U\L), hyperprolactinemia (89.3±4.87 U\L) and control (83.2±8.20 U\L) groups.

Results showed that ALP levels elevated significantly ($p \leq 0.05$) for obesity group in comparison with control.

Results showed that ALP levels elevated significantly ($p \leq 0.05$) for hyperprolactinemia group in comparison with control and not significantly with obesity group (figure 4.17, table 4.3).

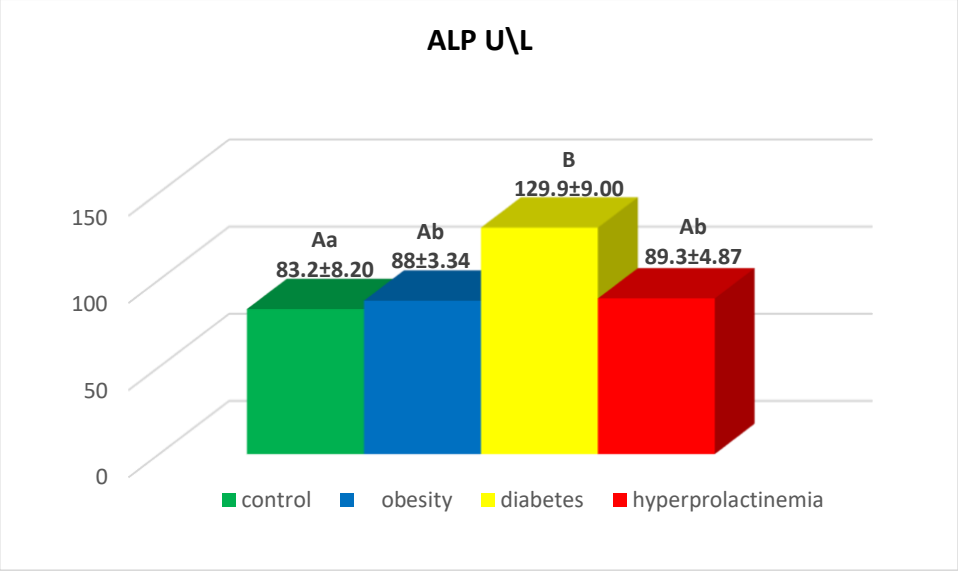


Figure (4.17): Changes of ALP enzyme levels of different study groups.

*Values are expressed as mean ± SD.

*Means followed by different capital letters are significantly different between groups at $p \leq 0.01$.

*Means followed by the same capital letters are not significantly different.

*Means followed by different small letters are significantly different between groups at $p \leq 0.05$.

*Means followed by the same small letters are not significantly different.

Table (4.3): CRP and liver enzymes changes during different study groups.

Parameters	Control	Obesity	Diabetes	Hyperprolactinemia
CRP mg/dl	1.50 ± 0.31^{A}	6.65 ± 0.94^{B}	4.56 ± 0.75^{C}	3.54 ± 0.56^{D}
ALT U/L	12 ± 1.44^{A}	16.75 ± 2.04^{Ba}	20.95 ± 2.24^{C}	15.45 ± 1.11^{Bb}
AST U/L	15.05 ± 1.93^{A}	16.10 ± 2.40^{A}	15.65 ± 1.49^{A}	18.5 ± 1.51^{B}
ALP U/L	83.2 ± 8.20^{Aa}	88 ± 3.34^{Ab}	129.9 ± 9.00^{B}	89.3 ± 4.87^{Ab}

*Values are expressed as mean ± SD.

*Means followed by different capital letters are significantly different between groups at $p \leq 0.01$.

*Means followed by the same capital letters are not significantly different.

*Means followed by different small letters are significantly different between groups at $p \leq 0.05$.

*Means followed by the same small letters are not significantly different.

Chapter Five

Discussion

5.1 Vitamin D

The present results showed that vitamin D levels decreased significantly ($p \leq 0.01$) in all groups of the study in comparison with the control (figure 4.1; table 4.1).

This decrease may be explained via the negative associations between current high levels parameters of each TSH, insulin resistance, calcium, CRP, ALT and ALP (figures 4.5, 4.11,4.13, 4.14, 4.15, 4.17;tables 4.1, 4.2, 4.3) and vitamin D. High levels of TSH may be considered an indicator of this deficiency due to the sensitivity decrease of thyroid hormones caused by this deficiency, furthermore ,insulin resistance might be reflected the carbohydrate metabolic disorders in the absence of the role of vitamin D and its action on regulate carbohydrate metabolism , moreover, the current reduction of calcium levels in all studied groups may be reflects the status of vitamin D and the decrease of absorption ability of calcium in these deficient vitamin D studied groups, furthermore,
the elevation of CRP might be represented an inflammation marker in deficient women of the current study groups (that consider as a low-grade inflammation) pointed the reduction of anti-inflammatory role of vitamin D, in addition, high levels of ALT and ALP might be induced downregulation for the vitamin D-25-hydroxylase activity, thus, the local conversion of this vitamin to its active form inside the liver cells be reduced.

Furthermore, high score of BMI (obesity) associated negatively with low levels of vitamin D as a result of the dilution or sequestration of this vitamin in adipose tissue, thereby, reducing the conversion ability for this vitamin from pre-vitamin to active vitamin D, moreover, in hyperprolactinemic women the high prolactin levels caused an impairment for different steps of vitamin D synthesis therefore, vitamin D deficiency.

The current results and concepts are in agreements with the findings of the following studies.

High concentrations of TSH are associated negatively with vitamin D deficiency, deficient women are more susceptible to metabolic disorders and impaired sensitivity to thyroid hormones (Zhou *et al*., 2023), in addition, Schleu and his coworkers (2021) found that patients with lower levels of vitamin D and obesity tend to present distinct higher values of TSH and HOMA-IR, moreover, elevated levels of TSH have been linked to decreased levels of pro hormone (25-OHD), a direct correlation has been shown between TSH and 25-OHD levels in individuals with T2DM, higher levels of 25- OHD with suppressed TSH levels may be attributed to enhanced absorption of 25-OHD in a hyperthyroid condition (Aslam, 2023).

Many studies have reported that vitamin D is negatively associated with HOMA-IR and an increase in the power of this correlation is linked with the highest BMI in women (Halalsheh *et al*., 2023; Yu *et al*., 2024), in addition, Usama and his team (2024) found that insulin resistance in vitamin D-deficient women was significantly higher than that in the non-deficient obese women.

Moreover, vitamin D deficiency is highly prevalent in diabetic women and is associated negatively with HOMA-IR (Sura *et al*., 2024; Yang,2024).

Many studies showed that vitamin D deficiency associated with decrease calcium levels (Kiran *et al*., 2014; Walia *et al*., 2017) due to the role of vitamin D for calcium absorption and minerals homeostasis (Bendotti *et al*., 2025).

Furthermore, obesity, diabetes and hyperprolactinemia are considered as a systemic low-grade inflammation, as demonstrated by increase circulating levels of inflammatory markers such as C-reactive protein (Chu *et al*., 2023; Baba *et al*., 2023; Domazet *et al*.,2024).

Krajewska and his team (2022) found that vitamin D supplementation seems to exert its anti-inflammatory effect mainly via decreasing of CRP level.

Mirza and his team (2022) showed that vitamin D deficiency was associated significantly with high levels of CRP in obese women, in addition, Shan and his team (2024) showed that vitamin D deficiency is widespread in diabetic women and associated with high levels of CRP which may be related to a decrease in 25(OH)D3 levels in the blood.

Furthermore, Bellastella and his colleagues (2021) suggested that ALP might be involved in the regulation of vitamin D-25-hydroxylase activity, in addition, vitamin D deficiency is associated with a higher risk of hepatic steatosis in obese women, low levels of vitamin D are associated with high levels of ALP and correction of vitamin D deficiency may have a beneficial role in the management of NAFLD in patients with obesity (He *et al*., 2020;Borges-Canha *et al*., 2021).

Vitamin D deficiency is highly prevalent in obese women and has a negative association with high levels of ALT (Esteghamati *et al*., 2014), in addition, Bakhuraysah and his coworkers (2023) found that vitamin D deficiency is common in diabetic women and associated with high levels of ALT, furthermore, Mozaffari and his colleagues (2021)showed that vitamin D supplementation decreased ALT and ALP levels possibly through decreasing HbA1C and hepatic ALT could improve diabetes complications.

Derbel and his colleagues (2024) showed that vitamin D deficiency is common in obese women and found that vitamin D levels were correlated with body fat mass due to hydrophobic characteristics, vitamin D can leave the circulation and end up being sequestered in the adipose tissue of obese people which explaining its low serum levels.

25(OH)D levels inversely correlate with body weight and body fat in obese people, dilution of ingested or cutaneously synthesized vitamin D in the large fat

mass of obese patients fully explains their typically low vitamin D status (Migliaccio *et al*., 2019).

Vitamin D deficiency is associated with high levels of prolactin in adolescent girls compared with those who have adequate levels of vitamin D due to the reduction of HPL impact on the 25-hydroxyvitamin D concentration that considered as a precursor for vitamin D synthesis (Krysiak *et al*., 2020; Amanzholkyzy *et al*., 2023).

Nevertheless, Paul and his colleagues (2019) found that serum 25(OH)D level showed no correlation with serum TSH level.

ElJilani and his colleagues (2021) showed that diabetic women with vitamin D deficiency had normal levels of ALP and ALT enzymes.

Saqib and his team (2018) found that deficient women did not have any direct impact on alkaline phosphatase.

5.2 Follicle-stimulating hormone (FSH)

The present results showed an increase tendency of FSH levels in all groups of the study (figure 4.2; table 4.1).

This increase seems to be associated with the current vitamin D deficiency (figure 4.1; table 4.1) and has detrimental effects on ovarian function due to the role of vitamin and its overlapping with both of FSH synthesis and their receptors regulation. Moreover, this elevation may be behind the high levels of current insulin resistance in all groups of the study via the influence of FSH action on present insulin secretion (figures 4.8, 4.11; table 4.1,4.2). Beside that, obesity group (high BMI score) has a harmful impact on different reproductive hormones including FSH that leading to many ovarian disorders. In addition, hyperprolactinemic women haven't supported the increment of FSH in this group

similarly with other groups of the study due to the inhibitive role of high current prolactin (figure 4.4; table 4.1) on gonadotropin-releasing hormones.

The current results and concepts are in agreements with the findings of the following studies.

Merhi and his team (2014) suggested that vitamin D alters anti-müllerian hormone (AMH) signaling and steroidogenesis in human cumulus GCs and it is possible that vitamin D alters a common intracellular pathway involved in the regulation of both AMH receptor- II and FSH receptor , in addition, Ersoy and his colleagues (2016) found that vitamin D increases AMH synthesis in granulosa cells and AMH reduces FSH levels by inhibiting the negative feedback of FSH synthesis.

Furthermore, low levels of vitamin D were associated with higher FSH levels, a biomarker of ovarian reserve, which suggests a decrease in primordial follicles and possible acceleration towards menopause (Jukic *et al*., 2015), in addition, Nikbakht and his team (2024) found that deficiency of vitamin D have an inverse relationship with FSH and vitamin D is important in infertile women, especially in patients with decreased ovarian reserve, moreover, Salahuddin and his colleagues (2024) found that vitamin D deficiency was prevalent in all infertile women and significantly associated with FSH, vitamin D has an indirect effect on follicular development and ovarian functions.

Moreover, high concentrations of FSH were associated with vitamin D deficiency in adolescents with obesity (Viana Pires *et al*., 2020), in addition, Bacanakgil and his team (2022) demonstrated that vitamin D supplementation reduces FSH levels and vitamin D might be considered as a fertility treatment for patients with diminished ovarian reserve and vitamin deficiency.

Aydin and his team (2024) found that FSH has significant metabolic roles beyond reproduction, involving insulin secretion and potentially contributing to

puberty-related hyperinsulinemia and insulin resistance , in addition, high serum FSH levels in pre-pubertal girls were associated with an increased risk of metabolic syndrome development during pubertal transition and a physiological increase in FSH levels through puberty, after reaching a critical point, FSH might start to stimulate insulin secretion and contribute to the physiological insulin resistance of puberty (Aydin *et al*.,2022),furthermore, Smaism and his coworkers (2016) found high concentrations of FSH associated with high levels of insulin resistance in diabetic women with PCOS.

Obesity in women of reproductive age is related to menstrual disorders, ovulation disorders, insulin resistance and the occurrence of infertility (Vigil *et al*., 2022),in addition , Seth and his team (2013) found that obesity is correlated with hormonal derangements which may be responsible for infertility and a significant positive correlation was observed between serum FSH and BMI in obese women ,moreover ,Alziyadi and his team (2024) showed that obese women had a significantly higher mean value of FSH compared to non-obese women and the correlation between BMI and FSH in women of reproductive age is of significant importance in the maintenance of a regular reproductive cycle.

Furthermore, Aishwarya and his team (2021) showed that FSH is associated with lipodystrophy of fat tissue and may tend to rise to higher levels when BMI increases, in addition, Liu and his team (2015) showed that FSH levels are positively correlated with changes in the BMI of women and suggested the possible role of high FSH levels in the increase in fat mass.

Bakare and his colleagues (2024) showed that persistent prolactin levels projected in HPL cause dysregulation of gonadotropin-releasing hormone neurons in the hypothalamus leading to decreased pituitary FSH and LH secretions, moreover, Su and his team (2011) found that obese women with HPL showed low levels of FSH and was associated significantly with prolactin levels,

additionally, Kubba and his team (2015) found that high prolactin levels are associated with low levels of FSH in hyperprolactinemic women.

Nevertheless, Altuntas and his team (2022) demonstrated no significant relationship between FSH and serum 25(OH) vitamin D levels in infertile deficient women.

Cai and his colleagues (2022) showed that insulin resistance was not associated with FSH levels in women without PCOS.

5.3 Estradiol

The present results showed a significant ($p \leq 0.01$) elevation of estradiol levels in all study groups (figure 4.3; table 4.1).

This elevation might be considered as a harmful and unbeneficial impacts according to its association with the current parameters such as vitamin deficiency, high levels of insulin resistance, FSH and prolactin in all the studied groups (figures 4.1,4.11,4.2,4.4; tables 4.1,4.2).

These above different parameters may be stand beyond the increase of estradiol levels in the present study via the role of vitamin D that regulates both of estradiol synthesis and receptors expression, moreover, present high estradiol might be caused high insulin resistance across its direct role on insulin secretion and biosynthesis, in addition, the present high levels of estradiol might be increased due to the present to high levels of FSH and its stimulation on ovarian follicles, besides that, obese women characterized with high conversion of androgens to estrogens by aromatase enzyme and more estradiol production that acts as prolactin stimulator leading for more prolactin secretion due to its inhibition role on dopamine secretion as occurred for the hyperprolactinemic women.

The current results and concepts are in agreements with the findings of the following studies.

High concentrations of estradiol represent one of the disorders of the menstrual cycle, as it increases endometrial growth, thus leading to heavy menstrual bleeding (Hapangama and Bulmer, 2016), moreover, women who exposure to high levels of both endogenous and exogenous estradiol are more likely to develop breast cancer (Mohanty *et al*., 2024), in addition , the influence on certain signaling processes involved in the pathogenesis of anxiety symptoms (Dutkiewicz *et al*.,2024).

Vitamin D may inhibit the growth of breast cancer cells through down-regulation of estradiol receptor expression and attenuation of estradiol signaling and synthesis (Krishnan *et al*., 2012).

Vitamin D deficiency is inversely correlated with high levels of estradiol in obese women with menstrual disorders that decline after vitamin D supplementation (Grzechocińska *et al*., 2018; Donayeva *et al*., 2023).

Al-Shaer and his coworkers (2019) indicated that vitamin D deficiency is highly prevalent in premenopausal women and associated with high levels of estradiol which decreased after vitamin D supplementation.

Estradiol plays a role in various insulin-sensitive tissues and organs by improving and/or modulating glucose homeostasis (De Paoli *et al*.,2021), in addition, long-term exposure to estradiol increases insulin, insulin gene expression and insulin release via the estrogen receptor α (ERα) (Soriano *et al*., 2011) and increased insulin gene expression associated with the concentration of estradiol (Vlachodimitris *et al*., 2020), furthermore, over estrogenic stimulation through ERα will produced excessive insulin signaling, in turn, leading to systemic insulin resistance (Nadal *et al*., 2009a).

Furthermore, estrogenic levels disturbance might interfere with normal metabolism therefore more insulin and insulin resistance occurred till the diabetic state (Nadal *et al*., 2009b), in addition, high levels of estradiol in both pre and diabetic women might be caused (partially) high insulin resistance (Şahin *et al*., 2020), moreover, estradiol exhibited positive associations with insulin and insulin resistance (Yeung *et al*.,2010).

FSH increase acts on the maturity and size of the follicles thus increases the secretion of estradiol (Patricio and Sergio,2019; Itriyeva, 2022).

In obese women who have high both adipose tissue and BMI, the conversion of androgens to estrogens be increased by aromatase enzyme (Giviziez *et al*., 2016), in addition, estradiol stimulates the replication of adipocyte precursors, thereby increases the estrogen synthesis (Ergasheva, 2024), furthermore, Emaus and his team (2008) showed that high level of estradiol might be combined with obese premenopausal women whom their BMI was high.

On the other hand, HPL most probably occurred by high levels of estradiol due to its inhibiting action on dopamine production and thereby prolactin stimulation (MohanKumar *et al*., 2011), in addition, rats prolactinoma formation was occurred after estradiol exposure via the inhibition routes of dopamine receptors in vitro (Sarkar,2006).

Nevertheless, Harmon and his team (2020) showed that vitamin D deficiency was associated with low levels of estradiol in young women.

5.4 Prolactin

The present results showed a significant increase of serum prolactin levels in all groups of the study (figure 4.4; table 4.1).

This increase may arise indirectly by the influence of the current vitamin deficiency (figure 4.1; table 4.1) on the current high levels of estradiol (figure 4.3; table 4.1) that plays (estradiol) a role in two routes: firstly by inhibiting dopamine action leading for more prolactin release, secondly by enhances the prolactin response to TRH which was proved by current high levels of TSH (figure 4.5; table 4.1), moreover, high accumulation of adipose tissue (obese women) have an ability to produce more prolactin.

The current results and concepts are in agreements with the findings of the following studies.

Vitamin D deficiency is highly prevalent in hyperprolactinemic adolescents and women with HPL (Krysiak *et al*., 2020; Amanzholkyzy *et al*., 2023), in addition, Krysiak and his coworkers (2015) showed that vitamin D deficiency associated with elevated macroprolactin levels in premenopausal women.

Vitamin D deficiency is inversely correlated with high levels of estradiol in obese women with menstrual disorders (Grzechocińska *et al*., 2018;Donayeva *et al*., 2023), in addition, Al-Shaer and his team (2019) found that vitamin D deficiency is highly prevalent in premenopausal women and associated with high levels of estradiol which decreased after vitamin D supplementation, moreover, vitamin D regulates estradiol receptors expression and attenuation of estradiol signaling and synthesis, thereby, vitamin D may inhibit the growth of breast cancer cells (Krishnan *et al*., 2012).

High levels of estradiol stimulate prolactin secretion via inhibiting dopamine production (MohanKumar *et al*., 2011), in addition, rats prolactinoma formation

occurred after estradiol exposure via the inhibition routes of dopamine receptors (Sarkar,2006).

Sanjari and his team (2016) showed that hyperprolactinemic women have high levels of estradiol that cause an increase in prolactin levels, in addition, Wazir and his coworkers (2024) found that high levels of TSH are quite prevalent in patients with high prolactin especially in women due to the enhancement role of estradiol on the prolactin response for exceed TRH.

Khan and his colleagues (2025) showed that high levels of TRH stimulate thyrotrophs cells to produce more TSH and thereby more prolactin levels, in addition, Sheikhi and Heidari (2021) showed that hyperprolactinemic women are frequently associated with high TSH concentrations.

In addition, Dardar and his team (2022) demonstrated that the prolactin levels were higher in obese women when compared to the non-obese women, furthermore, adipose tissue produced prolactin and expressed its receptor, also biologically active prolactin secreted by all adipose tissue in different locations such as breast, visceral and subcutaneous (Brandebourg *et al*., 2007).

5.5 Thyroid-stimulating hormone (TSH)

The present results showed that the TSH levels increased significantly in all studied groups (figure 4.5; table 4.1).

This elevation may reflects the negative effect of vitamin D deficiency (figure 4.1; table 4.1) due to the regulatory role of this vitamin for the pituitary thyrotropes and thyrocytes and/or across the increase of current estradiol levels (figure 4.3; table 4.1) that enhance the TRH to raises the TSH levels, moreover, the positive association between the current high levels of insulin resistance and the TSH increment in all studied groups (figure 4.11;table 4.2) may be detected

as a sign for different metabolic disorders, in addition , the absence of the anti-inflammatory role of vitamin D in all studied groups , these groups considered as a low grade inflammation (proved by high current levels of CRP (figure 4.14;table 4.3) and this CRP correlated positively with high levels of TSH , therefore inflammation effects (cytokines) may be contributed to abnormal thyroid hemostasis and increases TSH levels, furthermore, adipose tissue in obese women considered as additional factor that contributes in TSH increase via its impacts on both the reduction of TSH receptors and the increase of TRH stimulation, moreover, the high levels of TSH is a comping with hyperprolactinemic women due to the high levels of TRH release which stimulated by high current levels of estradiol.

The current results and concepts are in agreements with the findings of the following studies.

Many studies indicated that vitamin D deficiency associated with high TSH levels in obese, diabetic, and hyperprolactinemic women (Rostami *et al*., 2020; Abass, 2022; Amanzholkyzy *et al*., 2023), in addition, Safari and his coworkers (2023) showed that vitamin D supplementation reduces serum TSH in obese women with hypothyroidism.

Moreover, women with vitamin D deficiency are more susceptible to impaired thyroid hormones (Chen *et al*., 2023), in addition, Modi and Garg (2024) observed a positive significant association between vitamin D deficiency and the presence of thyroid disorders, also a significant negative association with TSH levels, furthermore, vitamin D may exhibit such regulatory effects via their receptors on both the pituitary thyrotropes and thyrocytes (Das *et al*., 2018), in addition, Barchetta and his team (2015) indicated that vitamin D might influenced the hypothalamus–pituitary–thyroid axis, by VDR expression on the hypothalamus and thyrotropic pituitary cells.

Benvenga and his colleagues (2018) found that estradiol stimulates the secretion of TSH even when the thyrotrophes are under negative feedback by thyroid hormones, in addition, Mijiddorj and his team (2012) showed that higher concentrations of estradiol potentiate the effects of TRH.

The prevalence of metabolic syndrome was significantly higher in women with high TSH levels (Teixeira *et al*., 2020), in addition, high levels of insulin resistance and high insulin levels were found to be positively correlated with high TSH levels in hypothyroidism women (Unnikrishnan *et al*., 2023), moreover, Muscogiuri and his team (2013) showed that the increase of insulin resistance might be played a pivotal role in the changes of thyroid homeostasis.

Obesity, diabetes and hyperprolactinemia are considered as a systemic low-grade inflammation, as demonstrated by increased circulating levels of inflammatory markers such as C-reactive protein (Chu *et al*., 2023; Baba *et al*., 2023; Domazet *et al*., 2024).

Hassan and Abbas (2022) found that high CRP levels were associated with high TSH levels in hypothyroidism women, in addition, Li and his coworkers (2022) found that increase levels of CRP were associated with increase levels of TSH and a causal association between CRP and thyroid signaling TSH and TSH levels could be positively affected by CRP levels, moreover, Kshetrimayum and his team (2019) found a significant positive association was found between high-sensitivity C-reactive protein (hs-CRP) and TSH levels in hypothyroidism women.

Furthermore, different cytokines such as IL6, IL10, IL17 and TNF-α were found in high levels in hypothyroidism women and these high levels of cytokines may enhance TSH levels (Baldissarelli *et al*., 2020; Croce *et al*., 2021).

Many studies found that adipose tissue may contribute to increase TSH levels in obese women (Sosa-López *et al*., 2021; Mele *et al*., 2022).

Obesity (adipose tissue) might played an important role in modifying the thyroid hormones and TSH receptors gene expression in adipose tissue (Nannipieri *et al*., 2009), in addition, De Pergola and his team (2007) showed that control of TSH secretion by free thyroid hormones is possibly impaired in obesity, moreover, leptin hormone regulates the production of TRH and increases the release of TSH (Teixeira *et al*., 2020), furthermore, Bétry and his team (2015) showed that TSH levels are significant positive associated with BMI and leptin hormone in obese women.

Wazir and his team (2024) found that high levels of TSH are quite prevalent in patients with high prolactin especially in women due to the enhancement role of estradiol on the prolactin response for exceeded TRH, in addition, Sheikhi and Heidari (2021) showed that hyperprolactinemic women are frequently associated with high TSH levels.

5.6 Triiodothyronine (T3) and Thyroxine (T4)

The present results increased during different groups of the study (figures 4.6,4.7; table 4.1).

The deficiency of vitamin D might be elevated the current TSH levels (figure 4.5 ; table 4.1) via the high current levels of both estradiol and CRP (figures 4.3,4.14;tables 4.1,4.3) thereby, increased the levels of T3 and T4, moreover, this deficiency might be worsened these findings of studied groups, furthermore, high current levels of liver enzymes (figures 4.15,4.16,4.17;tables 4.3) that reflected some liver disorders might be contributed in abnormal hemostasis of thyroid hormones, in addition, adipose tissue that accumulated in obese women might be attributed to the unbalance of these hormones, moreover, in hyperprolactinemic women, high TRH (proved by high present TSH) might be the main cause for this elevation of T3 and T4.

The current results and concepts are in agreements with the findings of the following studies.

Many studies indicated that levels of TSH, T3 and T4 increased in women with vitamin D deficiency (Aljabri, 2019; Zhou *et al*., 2023).

Chen and his team (2023) showed that high levels of thyroid hormones are associated with low levels of vitamin D and a high concentration of vitamin D could inhibit the secretion of TSH, thereby, reducing the secretion of both T3 and T4, in addition, Alrefaie and Awad (2015) found that vitamin D supplementation decreased T4 levels in diabetic rats via increased the expression of the deiodinase 2 enzyme that converted of T4 to T3.

Benvenga and his colleagues (2018) found that estradiol stimulates the secretion of TSH even when the thyrotrophes are under negative feedback by thyroid hormones, in addition, Mijiddorj and his team (2012) showed that higher concentrations of estradiol potentiate the effects of TRH.

Different studies showed that deiodinase activity reduced by the high levels of CRP, thus, the conversion of fT4 to fT3 be decreased leading to high levels of T4 (Shantha *et al*.,2009; Li *et al*., 2022).

Valdés and his coworkers (2017) showed that an increase in TSH levels associated with high levels of T3 in obese women due to deiodinase activity increases as BMI increases, in addition, De Pergola and his team (2007) found that levels of TSH and T3 increased in obese women due the control of TSH secretion by free thyroid hormones is possibly impaired in obesity.

Many studies have shown that high liver enzymes ALT, AST and ALP correlated positively with high levels of T3, T4 and TSH in women with thyroid disorders (Samir and Hameed, 2019; Hashim *et al*., 2023), in addition, Pandey and his colleagues (2013) found that highlevels of ALT and AST correlated positively with high levels of T3, T4 and TSH in women and liver disorder may

disturb thyroid hormones homeostasis, moreover, thyroid disorder might cause a significant impact on the metabolism of hepatocytes reflected by an increase in the AST, ALT and ALP in both hyperthyroidism and hypothyroidism women (Jalil *et al*., 2021).

Valvekar and his team (2016) found a positive association between high levels of prolactin and thyroid hormones T3 and T4 in hyperprolactinemic women, this association might have belonged to the common pathway (TRH) of TSH and prolactin secretion, in addition, Koner and his coworkers (2019) showed a positive correlation between prolactin levels and high TSH and FT4 levels in hyperprolactinemic women.

Nevertheless, different studies found that vitamin D deficiency is associated with low levels of T3 and T4 in women with thyroid disorders (Ebrahimabad *et al*., 2019; Ibrahim and El Shishtawy, 2024; Fang *et al*., 2025).

5.7 Insulin, glucose, HbA1C and insulin resistance

The present results increased during different groups of the study (figures 4.8,4.9,4.10,4.11; tables 4.1,4.2).

The deficiency of vitamin D and the metabolic abnormalities of the studied groups might be stand beyond these changes that concerning with glucose metabolism. Vitamin deficiency or and its effects on the current levels of estradiol , TSH and CRP (figures 4.3,4.5,4.14;tables 4.1,4.3) might be contributed to the glucose homeostasis disorder via its impacts on the beta cells and insulin secretion, moreover, cytokines (CRP) that released with high levels in the all of the studied inflammatory groups, adipose tissue in obese women and high levels of prolactin in hyperprolactinemic women might be contributed to drawing the metabolic picture of these parameters due to their stimulatory action on the insulin secretion.

The current results and concepts are in agreements with the findings of the following studies.

Different studies showed that vitamin D deficiency is associated negatively with high levels of insulin, glucose, insulin resistance and HbA1C in obese, diabetic and hyperprolactinemic women (Saleem *et al*.,2021; Krysiak *et al*., 2021; Arabi *et al*., 2024).

Vitamin D regulates insulin secretion of pancreatic β-cells (Szymczak-Pajor and Śliwińska, 2019) via their receptors found in pancreatic islets cells and the presence of VDRE in the promoter region of the insulin gene, additionally, vitamin D may also play a direct role in insulin secretion by regulating calcium fluxes in β-cells (Taneera *et al*., 2025), furthermore, Lontchi-Yimagou and his team (2020) showed that impaired insulin secretion and glucose intolerance occur following targeted disruption of VDRs or vitamin D-activating enzymes in various animal knock-out models.

Vitamin D deficiency is linked to an increase risk of developing T2DM, possibly due to its impact on glucose metabolism through β-cell function and insulin sensitivity (Darraj *et al*., 2019), moreover, Al-Qahtani and his colleagues (2024) demonstrated that vitamin D may plays potential roles in glycemic control and diabetes management, additionally, vitamin D supplementation initiated a marked improvement in tissue insulin sensitivity in patients suffering from metabolic syndrome (Nazarian *et al*., 2011), furthermore , vitamin D-deficient obese women had higher HOMA-IR levels, which decreased after vitamin D supplementation, thus, supplementation may be more beneficial for individuals with higher insulin resistance (Imga *et al*., 2019).

Vitamin D deficiency and elevated CRP levels were significantly associated with an increase risk of developing diabetes, that might be affected by inflammation (Kositsawat *et al*.,2025), furthermore, vitamin D has been shown

to reduce inflammatory cytokines, thereby protecting pancreatic beta cells and enhancing insulin secretion through regulating Ca^{2+} signaling (He *et al*., 2025).

Numerous studies have reported a positive association between high TSH levels and insulin resistance levels in women with thyroid dysfunction, which may contribute to the development of pancreatic β-cell dysfunction (Kocatürk *et al*., 2020; Allam *et al*.,2021;Yang *et al*., 2023), in addition, Zhou and his team (2024 a) suggested that high levels of TSH may be induce insulin resistance by disrupting insulin signal transduction and downregulation of GLUT4 expression, resulting in reduced glucose uptake.

Low-grade inflammation is a key driver of whole-body insulin resistance in the progression, leading to decrease the insulin sensitivity, furthermore, inflammation plays a crucial role in the development of insulin resistance through various cytokines that disrupt insulin metabolic actions in metabolic tissues (Ehrmann *et al*., 2025).

Several studies showed a positive association between high insulin levels, insulin resistance and high BMI in obese women (Wiebe *et al*., 2022; Uludağ *et al*., 2023), furthermore, obese women with high insulin levels and insulin resistance may exhibit a homeostatic adaptive response to increase adiposity and free fatty acids (Fryk *et al*., 2021), in addition, Boden, (2009) summarized that adipose tissue releases free fatty acids, which potentiate glucose-stimulated insulin secretion, this leads to a series of biochemical changes that ultimately impede insulin entry into cells, resulting in insulin resistance.

Immune cells in adipose tissue exhibit different pro-inflammatory properties that secrete pro-inflammatory cytokines which impaired insulin signaling that promoting the progression of insulin resistance (Arneth, 2024).

High prolactin levels are often linked with the high tissue's resistance to insulin (Gierach *et al*., 2022), moreover, Tuzcu and his colleagues (2009) found that

hyperprolactinemia associated with diferent metabolic abnormalities due to the prolactin disruption on glucose homeostasis. Furthermore, high levels of prolactin might be directly stimulated the insulin secretion and subsequently the whole-body of insulin resistance (Atmaca *et al*., 2013).

5.8 C- peptide

The present results showed that the C- peptide levels increased in all studied groups (figure 4.12; table 4.2).

These findings confirmed the previous results about the glucose metabolism (figures 4.8,4.9,4.10,4.11;tables 4.1,4.2) .The deficiency of vitamin D might be behind high C-peptide levels due to the role of vitamin D in regulation of beta cells function and insulin secretion, moreover, the metabolic and inflammatory dysregulation of the studied groups might be contributed to elevated C-peptide levels, which affect β-cell function and subsequently higher insulin secretion and insulin resistance, furthermore ,elevated C-peptide levels in hyperprolactinemic women associated with current high levels of insulin that be probably attributed to the stimulatory effect of high prolactin levels on insulin secretion, moreover, high C- peptide levels might be considered as a liver dysfunction marker due to the current high levels of liver enzymes (figure 4.15,4.16,4.17; table 4.3).

The current results and concepts are in agreements with the findings of the following studies.

Numerus studies demonstrated that high levels of C-peptide associated with glucose metabolism disorders, the C-peptide levels increased due to pancreatic beta cells response to insulin resistance that leading to increased insulin secretion, thereby contributing to loss of glycemic control and increased risk of developing diabetes (Abed, 2013; Zaki *et al*., 2018;Sosibo *et al*., 2024), moreover, Khan and his colleagues (2018) reported a significant correlation between C-peptide and

insulin resistance in both diabetic and nondiabetic women, suggesting that C-peptide may serve as a predictor for insulin resistance.

Many studies showed that vitamin D deficiency associated with the changes of C-peptide levels (Monapati *et al*., 2023;Xiang *et al*., 2024), moreover, Al-Qahtani and his team (2024) demonstrated that vitamin D deficiency is associated with low levels of fasting C peptide for the diabetic women due the beta cells unresponsive, furthermore, in diabetic patients sufficient levels of vitamin D act synergically with high levels C peptide to controlled the diabetes status possibly due to impact of vitamin D on glucose metabolism through the function of β-cells and insulin sensitivity.

High levels of C-peptide associated with high levels of CRP, this association suggests that these biomarkers may be useful in individuals identifying of developing T2DM (Gedebjerg *et al*., 2023; Lee *et al*., 2024).

Furthermore Akter and his team (2022) showed that high C-peptide levels associated positively with the metabolic syndrome, they mention that the high BMI was the most significant factor that influencing C-peptide levels for the development of these metabolic syndrome, moreover, elevated C-peptide levels are associated with high insulin resistance in obese women, suggesting that this elevation may be considered as a risk factor for T2DM (Gilsa *et al*., 2024),in addition, high C-peptide levels are often observed in obese individuals, likely due to insulin resistance, which requires high insulin levels (Cho *et al*., 2024), moreover, Pereira and his team (2024) observed a positive association between high levels of C-peptide and high BMI in obese women and this observation might be pointed that these obese women had decreased in their pancreatic size.

Elevated C-peptide levels associated with high AST and ALT levels in women with NAFLD and this elevation may be useful for screening or monitoring insulin resistance in NAFLD which reflecting impaired liver function (Huang *et al*.,

2023a; Fang *et al*., 2024), furthermore, Zhou and his team (2024 b) demonstrated that both high levels of C-peptide and insulin resistance has a significant predictive value impact on hepatic fibrosis in women with T2DM mellitus and NAFLD.

5.9 Calcium

The present results showed that the calcium levels decreased in all studied groups (figure 4.13; table 4.2).

This decrease possibly represents a clear reflects of vitamin D deficiency due to the crucial role of vitamin D to regulating the calcium absorption, in addition, metabolic disorders, inflammatory state and high levels of ALP for all studied groups might be attributed for this decrease, furthermore, current thyroid hormones disruption (figures 4.6,4.7; table 4.1) that caused by vitamin D deficiency might be contributed of these calcium regulation abnormalities.

The current results and concepts are in agreements with the findings of the following studies.

Different studies demonstrated that vitamin D deficiency contributed for the reduction of calcium levels (Walia *et al*., 2017; Kandhro *et al*., 2019). Vitamin D plays important role for calcium absorption and minerals homeostasis (Bendotti *et al*.,2025), via its stimulation of the intestinal calcium-binding proteins production and augments blood calcium levels (Xu *et al*., 2024).

Tobias and his colleagues (2023) showed that the reduction in calcium levels associated positively with vitamin D deficiency in obese women, in addition, Shahwan and his colleagues (2019) showed that the decrease of calcium levels correlated with vitamin D deficiency in obese women, moreover, vitamin D levels

showed a significant positive association with calcium levels in diabetic women (Agrawal *et al*., 2019; Yasin *et al*., 2024).

Furthermore, supplementation intake of vitamin D plus calcium was associated with a lower risk of T2DM, suggests that increased vitamin D intake may potentiate the effect of calcium intake and supplementation with vitamin D plus calcium may improve insulin sensitivity (Kirii *et al*., 2009;Gagnon *et al*., 2014), in addition, Sergeev and Song (2014) showed that levels of vitamin D and calcium increase after supplementation of vitamin D plus calcium and this increase associated with activation of Ca2+-mediated apoptotic pathway in adipose tissue of obese mice .

Furthermore, Baek and his colleagues (2017) demonstrated that high serum calcium levels associated with decreased incident metabolic syndrome in individuals with obesity, in addition, Zhang and his team (2019) showed that calcium has anti-obesity effects and suggests the potential application of dietary calcium for prevention of obesity, moreover, Sun and his team (2012) showed that calcium intake may be contributes with combating obesity by its potential decrease of both intracellular lipid content and adipogenesis in mice.

Ali and his colleagues (2023) showed that calcium levels decrease in diabetic women, in addition, physiological calcium found to be vital for the proper functioning of the pancreatic β-cells and insulin releasing (Klec *et al*., 2019).

High pro-inflammatory cytokines associated with decrease of circulating calcium levels due to upregulate expression of calcium-sensing receptor that altered calcium homeostasis (Hendy and Canaff, 2016).

High levels of ALP that associated with low levels of calcium might exerts a critical function in modulating calcium absorption and utilization, the inadequate calcium absorption and excessive excretion might be changed the activity of ALP (Xu *et al*., 2024).

Sridevi and his team (2016) showed that thyroid hormones regulate mobilization of calcium and phosphorous into the blood and their clearance through urinary excretion, in addition, numerous studies demonstrate that thyroid hormones disorders are associated with changes in blood calcium levels due to their impact on bone reabsorption and release of calcium into the bloodstream (Jha *et al*., 2021; Turanjanin *et al*., 2024).

On the other hand, different studies demonstrated that vitamin D exert its effect synergistically with the cooperation of other hormones that related with calcium hemostasis such as parathyroid hormone and calcitonin (Masood and Mahmood, 2010; Saqib *et al*., 2018).

5.10 C-reactive protein (CRP)

The present results showed that the CRP levels increased significantly in all studied groups (figure 4.14;table 4.3).

Vitamin D deficiency might be explained this increase due to the anti-inflammatory role of this vitamin, in addition, these groups considered as a low-grade inflammation which might be contributed of this increase, furthermore, the CRP response might be enhanced by high levels of pro-inflammatory cytokines that associated with both of obese and diabetic women, similarly, in hyperprolactinemic women, prolactin acted as a pro-inflammatory factor thereby increased the CRP, besides that there is a mutual relationship between CRP and insulin resistance, the current elevation of insulin resistance(figure 4.11; table 4.2) at the all studied groups might be reduced the anti-inflammatory impact of the insulin hormone that might be supported the responsiveness of CRP levels

The current results and concepts are in agreements with the findings of the following studies.

Different studies demonstrated that vitamin D deficiency associated negatively with CRP levels (AbdElneam *et al*., 2024; Holmannova *et al*., 2025), in addition ,vitamin D supplementation seems to exert its anti-inflammatory effect mainly via decreasing of CRP level (Antwi *et al*., 2024), moreover, the production of pro-inflammatory cytokines decreased after vitamin binding to its receptors in monocytes, thus, vitamin D helps in reducing the concentrations of CRP and other inflammatory markers (Colin *et al*., 2010).

Vitamin D deficiency showed a negative association with inflammatory markers (including CRP) in obese, diabetic and hyperprolactinemic women (Fenercioglu *et al*., 2023; Krysiak *et al*., 2023; Murugiah *et al*., 2024).

Dwivedi and his team (2025) demonstrated that vitamin D supplementation significantly reduces inflammatory cytokines TNF-α and IL-6 in diabetic women, supporting its beneficial role in managing inflammation.

High levels of hs-CRP prevalence in deficient women might be contributed to cardiovascular risk (Dev *et al*.,2025; Kumar *et al*., 2025).

Obesity, diabetes and hyperprolactinemia considered as a low-grade inflammation that demonstrated by increased circulating levels of inflammatory markers such as C-reactive protein (Chu *et al*., 2023; Baba *et al*., 2023; Domazet *et al*., 2024).

Many studies showed that the CRP levels increased in obese women (Cohen *et al*., 2021; Toğuç, *et al*., 2025), in addition, the increase of fat-tissue mass enhances presence of each pro-inflammatory variants of macrophages, major sources of TNF-α and other inflammatory mediators which contributed in high levels of CRP (Bakinowska *et al*., 2024).

Different studies pointed that diabetic and progression of associated with several inflammatory biomarkers including CRP (Okdahl *et al*., 2022;Khattab *et al*., 2022), moreover, Guest and his (2008) showed that pro-inflammatory more prevalence than the anti-inflammatory cytokines in T2DM individuals, in addition, long-term exposure to high levels of glucose significantly enhanced the increase production of pro-inflammatory cytokines, including tumor necrosis-α, and IL-6(Suzuki *et al*., 2021),furthermore, high levels of CRP might be indicated for the association between pro-inflammatory cytokines and etiology of T2DM (Bahgat and Ibrahim, 2020).

Prolactin accounted as a pro-inflammatory mediator that promoted inflammatory pathological of cells and tissues in hyperprolactinemic individuals (Rasmi *et al*., 2023), in addition, Shen and his colleagues (2023) found that CRP was significantly higher in women with high prolactin levels, furthermore, Zaidalkilani and his coworkers (2024) showed that elevated levels of prolactin correlated with inflammation markers increase in women with prolactinoma , moreover, different authors mentioned that hyperprolactinemia associated with low-grade inflammation independently of BMI (Serri *et al*., 2006;Baba *et al*., 2023).

The increment of CRP levels associated with high HOMA-IR levels (Drabsch *et al*., 2018), in addition, the dysregulation of glucose homeostasis leading to high insulin resistance that disrupted the insulin signaling and diminished the anti-inflammatory effects of insulin action, thereby, the elevation of CRP levels (Missel *et al*., 2021).

5.11 Alanine transaminase (ALT), Aspartate transaminase (AST) and Alkaline phosphatase (ALP)

The liver enzymes (ALT, AST and ALP) appeared an increase tendency during different groups of the study (figures 4.15, 4.16,4.17; table 4.3).

The deficiency of vitamin D, the metabolic and inflammatory abnormalities of the studied groups might be the main causes for this increase tendency. The consequently effect of vitamin D deficiency on the current levels of insulin, insulin resistance and CRP (figures 4.8,4.11,4.14; tables 4.2,4.3) leading to the impairment of insulin action thereby the increase of these enzymes, moreover, the metabolic and inflammatory abnormalities of the studied groups might be enhance the liver's fat accumulation and increase the liver enzymes, in addition, hyperprolactinemic women have more increase of these enzymes according to the role of high levels of prolactin on the detrimental effect on insulin secretion, furthermore, the current high levels of TSH during groups of this study added another evidence related with this increase of enzymes via their effects on the liver and metabolism .

The current results and concepts are in agreements with the findings of the following studies.

Numerous studies demonstrated that vitamin D deficiency associated with high levels of ALT, AST and ALP in obese and diabetic women (He *et al*., 2020; Fang *et al*., 2024) due to the adverse effects of vitamin D deficiency on human liver function (Skaaby *et al*., 2014).

Furthermore, vitamin D deficiency considered as an independent risk factor for the liver enzyme's increase and the occurrence of liver diseases in obese and diabetic women (Borges-Canha *et al*., 2021;Ciardullo *et al*., 2023) , in addition , vitamin D deficiency might be potentiated the adverse effects of obesity and diabetes on liver functions via its impairment of the lipid clearance by the liver ,

worsening the insulin resistance impact and increasing the inflammatory cytokines mediators … that affected all together the liver functions thereby the elevation of these enzymes (Bima *et al*., 2021;Yu-Lei *et al*., 2024).

Different studies indicated that vitamin D supplementation associated with the reduction of the liver enzymes in obese, diabetic women and women with abnormal liver function (Amiri *et al*., 2016; Hussain *et al*., 2019; Mansour - Ghanaei *et al*., 2020), moreover, Mozaffari and his team (2021) showed that vitamin D supplementation possibly through HbA1C and ALT levels that improves diabetes complications.

Obesity and metabolic disorders including T2DM have a detrimental effect on liver functions thereby increased their enzymes (Huang *et al*., 2023 b) , moreover, insulin resistance that accounts as a risk factor for liver enzyme 's increase in obese and diabetic women (Liu *et al*.,2021;Villasis-Keever *et al*., 2024),might be directly lead to both of lipotoxicity formation and lipolysis activation that enhanced the liver's fat accumulation and increased these enzymes (Parker, 2018), in addition, the low levels of adiponectin hormone that caused by obesity leads to storage of excess lipid in the liver and elevated the liver enzymes (Buechler *et al*., 2011;Gunjal *et al*., 2014).

The association between both the high levels of liver enzymes and CRP in women with metabolic syndrome (including obesity and diabetes) represents a strong predictor of metabolic syndrome (Islam *et al*., 2020; Ghani *et al*., 2023), furthermore, the overproduction of pro-inflammatory cytokines might played an important role in the liver's damage progression thereby liver enzymes elevation (Poniachik *et al*., 2006).

Hyperprolactinemia might be considered as a marker of chronic liver diseases due to the impairment of liver functions and a reduction of dopamine

concentration, thereby a high level of prolactin secretion (Rao *et al*., 2023; Babu *et al*., 2024; Kamath *et al*., 2025).

Thyroid disorders correlated positively with the increase of liver enzymes due to the thyroid hormones abnormalities that changed liver's functions and leading for more increment of these enzymes (Ajala *et al*., 2013; Kaur *et al*., 2024), furthermore, there is a positive association between high levels of both TSH and liver enzymes which pointed out the modulating role of TSH in intrahepatic lipid metabolism (Sileo *et al*., 2025).

Chapter Six

Conclusions and Recommendations

6.1. Conclusions

The results of the present study included the following conclusions:

1. There is a close mutual relationship between vitamin D deficiency and metabolic disorders.

2. Vitamin D deficiency may be influence the hypothalamic-pituitary ovarian axis, thereby disrupted the women's reproduction and in the same manner disrupted the metabolic reaction via hypothalamic-pituitary-thyroid axis.

3. Vitamin D deficiency associated with high unbeneficial prolactin secretion in women with metabolic abnormalities especially the hyperprolactinemia.

4. Vitamin D deficiency exacerbates the imbalance of glucose metabolism in obese, diabetic and hyperprolactinemic women, thereby vitamin D represent as a regulatory agent for glucose hemostasis.

5. Vitamin D deficiency worsens the inflammatory state of obese, diabetic and hyperprolactinemic women which they considered as low-grade inflammation in origin, therefor vitamin D accounts as an anti-inflammatory factor.

6. Vitamin D deficiency may be associated with various cellular physiological abnormalities according to lack of calcium absorption which interferes with these cellular physiological processes.

7. Vitamin D deficiency synergistically targeted (with the metabolic group's disorders) the liver which is the main metabolic center as evidenced by high levels of liver enzymes, thereby decline the liver abilities.

6.2. Recommendations

The author recommends the following:

1. Further studies with more samples and with other vital parameters related with vitamin D deficiency in women with different mensural cycle stages and different metabolic syndrome.

2. Studying the role of vitamin D and its deficiency related with the immune system and the anti-inflammatory actions as a regulator and a modulator for the immune cells and some immunological parameters.

3. Investigating the role of vitamin D and its deficiency on different hormonal secretion and pathways that modulate the various aspects of reproduction and fertility both in male and female of human being.

4. Examining the therapeutic and physiological aspects of vitamin D supplementation on individuals that attacked with metabolic syndrome.

5. Evaluation the role of vitamin D and its deficiency on some neurological and behavioral phenomena in elderly people.

6. Exploring and discussion the role of vitamin D as promoter and/or inhibitor agent on the molecular field such as a gene expression, cell division, apoptosis …. etc.

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Appendix

استمارة استبيان خاصة ببحث الطالبة فرح كاظم علوان

رقم العينة:

محل وتاريخ الولادة:

الحالة الاجتماعية: متزوجة غيرمتزوجة

في حالة الإجابة (متزوجة) هل لديك أطفال

عنوان السكن:

رقم الهاتف:

هل سبق وان اصبت بأحد الامراض المزمنة مثل ارتفاع ضغط الدم او السكري نعم كلا

هل سبق وان أجريت عمليه جراحية: نعم كلا

هل تستخدمين موانع الحمل الهرمونية او غير الهرمونية:

هل دورتك الشهرية منتظمة: نعم كلا

في حالة الإجابة (بكلا) ماهي علامات عدم الانتظام

هل سبق وان اصبت بمتلازمة تكيس المبياض : نعم كلا

هل انت من المدخنين:

هل توافقين على عملية سحب الدم لمرة واحدة خلال الطور الحويصلي من الدورة الشهرية:

هل توافقين على الانضمام الى عينة البحث: نعم كلا

علما بان لك الحق في الانسحاب من اكمال هذه المهمة وقت ماتشائين

الاسم الكامل والتوقيع والتاريخ

الخلاصة

تهدف الدراسة الحالية إلى معرفة علاقه نقص فيتامين دي ببعض المعايير الهرمونية والبيوكيميائية لدى النساء المصابات بالسمنة، السكري (النوع الثاني) وفرط البرولاكتين في محافظة ميسان، أجريت الدراسة في بعض مستشفيات المحافظة، مركز السكري والغدد الصماء وبعض المختبرات الطبية الخاصة، للمده من تشرين الثاني ٢٠٢٣ ولغاية أيار ٢٠٢٥.

شملت عينات الدراسة على 80 امرأة (أعمارهن بين 30 - 40 سنة)، مقسمة على أربع مجاميع رئيسية (20 امرأة / مجموعة)، على النحو الاتي:

- مجموعه السيطرة
- مجموعه السمنة
- مجموعه السكري (النوع الثاني)
- مجموعه فرط البرولاكتين

أظهرت النتائج ما يأتي:

1. انخفض فيتامين دي بشكل معنوي (أ≤ ٠.٠١) في المجاميع المدروسة مقارنة مع مجموعه السيطرة.
2. ارتفع مستوى الهرمون المحفز للجريبات وهرمون الاستراديول بشكل معنوي (أ≤ ٠.٠١) (عدا الهرمون المحفز للجريبات حيث ارتفع بشكل غير معنوي في مجموعة فرط البرولاكتين) في المجاميع المدروسة مقارنة مع مجموعة السيطرة.
3. ارتفع مستوى هرمون البرولاكتين بشكل معنوي (أ≤ ٠.٠٥) في مجموعتي السمنة والسكري وبمستوى (أ≤ ٠.٠١) في مجموعة فرط البرولاكتين مقارنة مع مجموعة السيطرة.
4. ارتفع الهرمون المحفز للغدة الدرقية بشكل معنوي (أ≤ ٠.٠١) وهرمون ثلاثي يوديد الثيرونين بشكل غير معنوي وهرمون الثيروكسين بشكل معنوي (أ≤ ٠.٠١) (عدا مجموعة السكري حيث ارتفع بشكل غير معنوي) في المجاميع المدروسة مقارنة مع مجموعه السيطرة.
5. ارتفع هرمون الأنسولين والببتيد-سي بشكل معنوي (أ≤ ٠.٠١) في مجموعتي السمنة وفرط البرولاكتين وبشكل غير معنوي في مجموعه السكري مقارنه مع مجموعه السيطرة.
6. ارتفعت مقاومة الأنسولين بشكل معنوي (أ≤ ٠.٠١) في مجموعتي السمنة والسكري وبمستوى (أ≤ ٠.٠٥) في مجموعه فرط البرولاكتين ومقارنه مع مجموعه السيطرة.

7. ارتفع الجلوكوز والهيموجلوبين السكري بشكل معنوي (أ≤ ٠.٠١) في مجموعه السكري وبشكل غير معنوي في مجموعتي السمنة وفرط البرولاكتين مقارنه مع مجموعه السيطرة.
8. ارتفع مستوى البروتين التفاعلي - سي بشكل معنوي (أ≤ ٠.٠١) في المجاميع المدروسة مقارنة مع مجموعة السيطرة.
9. انخفض عنصر الكالسيوم بشكل غير معنوي في المجاميع المدروسة مقارنة مع مجموعة السيطرة.
10. ارتفع انزيم الالانين امينو ترانسفريز بشكل معنوي (أ≤ ٠.٠١) في المجاميع المدروسة مقارنه مع مجموعه السيطرة.
11. ارتفع إنزيم أسبارتيت امينو ترانسفريز بشكل معنوي (أ≤ ٠.٠١) في مجموعة فرط البرولاكتين وبشكل غير معنوي في مجموعتي السمنة والسكري مقارنةً مع مجموعة السيطرة.
12. ارتفع إنزيم الفوسفاتيز القلوي بشكل معنوي (أ≤ ٠.٠٥) في مجموعتي السمنة وفرط البرولاكتين وبشكل معنوي (أ≤ ٠.٠١) في مجموعة السكري مقارنةً مع مجموعة السيطرة.

تمت مناقشة الابعاد الفسيولوجية لهذه النتائج وفقًا لتأثير نقص فيتامين دي المرتبط باضطرابات التمثيل الغذائي والالتهابي وبما تمثله مجاميع الدراسة، الامر الذي يودي الى تأثيرات ضارة متنوعة على المعايير الهرمونية والكيميائية الحيوية للمجاميع المدروسة.

الخـــلاصـــة

وزارة التعليم العالي والبحث العلمي
جامعة ميسان
كلية العلوم
قسم علوم الحياة

نقص فيتامين دي وعلاقته ببعض المعايير الهرمونية والبايوكيميائية في النساء البدينات المصابات بداء السكري النوع الثاني وفرط البرولاكتين في محافظة ميسان

رسالة مقدمة
الى مجلس كلية العلوم / جامعة ميسان
وهي جزء من متطلبات نيل درجة الماجستير علوم في علوم الحياة

من قبل

فرح كاظم علوان
بكالوريوس علوم حياة (2020)

بإشراف

الأستاذ الدكتور أحمد عبود خليفة

سبتمبر 2025م ربيع الاول 1447هـ