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Association between Vitamin D level and some physiological and biochemical parameters in pre and post menopause type 2 diabetic patients

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Abstract : This study aimed to evaluate the role of vitamin D and Estradiol hormone in the development of diabetes disease and their effect in pre and post-menopausal females. The hormones including (Estradiol and Insulin) and the physiological parameters (Vitamin D, Hemoglobin A1c, Fasting Blood Glucose, insulin resistance, insulin sensitivity, systolic and diastolic blood pressure). This case-control study was done in a period of March 2016 to October 2016 ,where the samples collected from Al-Sadr Teaching Hospital in Najaf Province. The number of samples was (80) patients with type 2 diabetes with an average age (36-65 year), all of them were with type 2 diabetes are divided to premenopausal and post menopause, Also, the study included 40 apparently healthy people with an average age (36-65 year) , as control matched with disease group. According to the comparison of premenopausal and postmenopausal women in both diabetic patients and in control group, the results showed significant ($p \leq 0.05$) elevation in Estradiol hormone level rates, Insulin hormone level rates and insulin resistance in both groups. On the other , the comparison of premenopausal patients with diabetic and premenopausal control groups the statistical analysis showed significant elevation ($p \leq 0.05$) in Hemoglobin$_{A1c}$ levels rate (HB$_{A1c}$), fasting blood glucose (FBG), Estradiol hormone level rates, Insulin hormone level rates, insulin resistance ,insulin sensitivity and diastolic blood pressure. According to the comparison of postmenopausal diabetic patients and postmenopausal control group, there were significant differences ($p \leq 0.05$) in Hemoglobin$_{A1c}$ levels rate (HB$_{A1c}$), fasting blood glucose (FBG), Estradiol hormone level rates, Insulin hormone level rates, insulin resistance and insulin sensitivity. In post-menopausal control group a significant negative correlation has been found between vitamin D and fasting blood glucose (FBG) level. In both premenopausal and postmenopausal diabetic patients and control group there were highly significant negative correlation between Insulin and insulin sensitivity, while highly significant positive correlation with insulin resistance. In post-menopausal diabetic patients, there were significant negative correlation between insulin and HBA1c. According to premenopausal control group, there were highly significant positive correlation between hemoglobinA1c (HBA1c) and fasting blood glucose FBG, while significant inverse correlation with insulin sensitivity. On the other hand, in premenopausal and postmenopausal diabetic patients groups there were highly significant positive correlation between hemoglobinA1c (HBA1c) and fasting blood glucose (FBG).

Introduction

The type 2 diabetes represent complex disease which results from the combination between behavioral ,genetic, and environmental factors [1] It is distinguished by insulin resistance represented by inability of the body to use insulin effectively and inadequate insulin secretion from pancreas resulting in high blood glucose levels (hyper glycaemia)[2,3]. Vitamin D is naturally found as ergocalciferol (vitamin D2) in edible fungus, while the colecalciferol (vitamin D3) synthesized in the skin via sun light exposure, and also is available through fish oils extracted from fish live in cold and deep water such as salmon and tuna [4,5].It is estimated that 80% to 90% of vitamin D in the body are produced by skin synthesis, and the remaining through the ingestion of foods and supplements of this vitamin [6]. In last years, vitamin D deficiency considered a public health problem in the world, because of its implications with the development of various diseases, among them DM2, hypertension and obesity [7]. In recent studies, it suggested that the polymorphism of the VDR gene can grant genetic protection against DM1, and the polymorphism of the CYP27B1 gene has effect in the susceptibility for the DM1 [8].

Menopause occurs when women stop producing female hormones and stop ovulating. Typically, it occurs when women older than 50 years. During menopause, women are going to develop many physiological changes and some diseases become more prevalent in postmenopausal women, including cardiovascular disease, osteoporosis, cancers of the vagina and uterus, and altered cognitive function [9].

One of the physiological changes which occur during menopause is the increase in body weight [10]. During the first years of endogenous estrogen decline, Postmenopausal women tend to experience an accelerated weight gain [11]. With increasing postmenopausal woman age, the lean body mass decreases while fat mass increases, commonly in the abdominal area [12].

Postmenopausal women with the diabetes disease have elevated dyslipidemia compared with non -diabetic women. Among diabetic women, patients that use hormone replacement therapy (HRT) had significant different glucose and lipid control levels than those who never had used HRT. Diabetic and non-diabetic postmenopausal women actually taking (HRT) have better lipoprotein profile than those never or previous users of (HRT) [13]. Estrogen deficiency is associated with a rapid reduction in bone mineral density. The incidence of osteoporosis increases after menopause, and the prevalence of osteoporosis is increasing with the recent increase in the elderly population [14,45]. Estrogen blocks the absorbing activity of osteoclasts, enhances the trans-intestine transportation of calcium, increases the absorption of calcium from kidneys and protects the osteoclasts. But after menopause, because there is a lack of ovarian function and estrogen, the activity of osteoclasts and the pace of bone destruction increases, which will result in 25-30% destruction in bone mass during a 5-10 years period [15]. Vitamin D can have significant influence on postmenopausal women, Improving the postmenopausal problems through several mechanisms including Its role as a substantial suppressor of the renin–angiotensin system (RAS) and is fundamental to maintain the normal cardiovascular homeostasis because of lower blood pressures [16,46].

Materials and methods

Study Population

The study subjects comprised from 80 patients suffer from type 2 diabetes randomly selected from AL-Sader Teaching Hospital (females), the control group study included 40 female apparently healthy and this group matched with patient group, both groups divided into pre and post menopausal groups. All subjects in this study were taken consent before participation in this study.

Blood Pressure

Measurement of arterial blood pressure for each patient in the sittingposition by using Mercury sphygmomanometer two additional times, waiting a five minutes between measurements and then take the reading average.

Collection of the blood samples

Venous blood samples were drawn from patient and control subjects using disposable syringes (5mL) in the sitting position. Five ml of blood were obtained from each subject by vein puncture , one ml was placed into EDTA tubes and the remaining 4 ml pushed slowly into disposable serum tubes containing separating gel . The blood in the EDTA tubes stored in - 20˚C in order to be used later in genetic part of the study , while blood in the gel containing tubes was allowed to clot at room temperature for 10-15 minutes and then centrifuged at 2000 × g for approximately 10-15 minutes then the sera were obtained and stored at -20˚C until analysis (hormonal assays).

Determination of fasting blood glucose (FBG)

The RanDox kit was used to determine serum Glucose levels and It is based on the PAP enzymatic determination of glucose [17].

Glycohemoglobin procedure assay

The hemoglobin A1c calculated as the following equation:

$$\text{Hemoglobin A1c \%} = \frac{Agly}{Atot} * concentration\ of\ standard * 7.6$$

Estradiol Assay Procedure

Done according to CALBIOTECH kit No. ES180S.

Insulin Assay Procedure

Done according to CALBIOTECH kit No IS130D.

Determination of insulin resistance

Insulin resistance is evaluated by determination of homeostasis model assessment of insulin resistance (HOMA-IR) [18].

3.4.4.2 Determination of insulin sensitivity

The quantitative insulin sensitivity check index (***QUICKI***) is derived using the inverse of the sum of the logarithms of the fasting insulin and fasting glucose [19].

Vitamin D Assay Procedure

Done according to CALBIOTECH kit No. VD220B.

Results

Level rates of some physiological and biochemical parameters in type 2 diabetic patients and control between pre and post menopause.

In premenopausal patients with diabetic and premenopausal control groups the statistical analysis showed significant elevation ($p \leq 0.05$) in Hemoglobin$_{A1c}$ levels rate (HB$_{A1c}$), fasting blood glucose (FBG), Estradiol hormone level rates, Insulin hormone level rates, insulin resistance ,insulin sensitivity and diastolic blood pressure. In postmenopausal diabetic patients and postmenopausal control group the statistical analysis showed significant differences ($p \leq 0.05$) in Hemoglobin$_{A1c}$ levels rate (HB$_{A1c}$), fasting blood glucose (FBG), Estradiol hormone level rates, Insulin hormone level rates, insulin resistance and insulin sensitivity. On the other hand, the statistical analysis of premenopausal and postmenopausal women in both diabetic patients and in control group showed significant differences in Estradiol hormone level rates, Insulin hormone level rates and insulin resistance in both groups. as shown in table (1).

Table (1) Level rates of some physiological and biochemical parameters in type 2 diabetic patients and control between pre and post menopause

Parameters	(Mean ± SD) Control group		Diabetic patients		Between groups	
	Pre menopause	Post menopause	Pre menopause	Post menopause	P-value pre-pre	p-value post-post
HBA1c	4.75± 0.92	4.56± 0.76	7.66± 1.52	7.48± 1.25	0.00*	0.00*
P-value within group	0.55		0.67			
FBG (mg/dl)	89.67± 13.58	92.93± 18.71	205.58± 70.38	191.10± 66.15	0.00*	0.00*
P-value within group	0.58		0.50			
Vitamin D (ng/ml)	16.73± 5.24	18.28± 3.35	19.36± 4.43	18.53± 4.49	0.21	0.19
P-value within group	0.40		0.73			
Estradiol (pg/ml)	181.34± 58.60	72.05± 27.12	126.03± 83.42	48.15± 31.15	0.04*	0.02*
P-value within group	0.00*		0.00*			
Insulin (µIU/ml)	5.02± 1.23	2.17± 1.17	15.10± 6.05	7.90± 2.59	0.00*	0.00*
P-value within group	0.00*		0.00*			
Insulin resistance	0.48± 0.15	0.98± 0.30	3.14± 1.04	8.14± 3.50	0.00*	0.00*
P-value within group	0.00*		0.00*			
Insulin sensitivity	0.44± 0.20	0.42± 0.09	0.36± 0.09	0.30± 0.11	0.03*	0.04*
P-value within group	0.74		0.053			
Systolic pressure (mm Hg)	116.11± 15.77	119.16± 14.43	128.33± 18.50	126.45± 13.75	0.06	0.10
P-value within group	0.59		0.69			
Diastolic-pressure (mm Hg)	72.77± 12.74	76.66± 9.84	84.16± 7.92	81.04± 7.78	0.01*	0.10
P-value within group	0.37		0.22			

(Mean ± SD): Mean± Standard Deviation ; * : significant at P value (≤0.05)

Correlation analysis between Vitamin D (ng/ml)and some physiological and biochemical parameters in pre and post menopause type 2 diabetic patients and control group.

In post menopausal control group a significant negative correlation has been found between vitamin D and fasting blood glucose (FBG) level as shown in figure (2).

Table (2) Correlation analysis between Vitamin D (ng/ml)and some physiological and biochemical parameters in pre and post menopause type 2 diabetic patients and control group.

Vitamin D (ng/ml)								
Parameters	Control group				Diabetic patients			
	Pre menopause		Post menopause		Pre menopause		Post menopause	
	r value	P value	r value	P value	r value	P value	r value	P value
Age	-0.070	0.805	0.310	-0.486	-0.178	0.561	-0.084	0.575
HBA1c	0.313	0.257	-0.496	0.121	-0.350	0.241	-0.203	0.171
FBG (mg/dl)	0.054	0.849	-0.711	0.014*	-0.182	0.552	-0.027	0.855
Estradiol (pg/ml)	0.381	0.161	0.032	0.925	0.082	0.800	0.171	0.299
Insulin (μIU/ml)	-0.090	0.759	0.479	0.161	-0.259	0.417	-0.076	0.619
Insulin Resistance	-0.086	0.771	-0.282	0.400	-0.398	0.201	-0.015	0.923
Insulin sensitivity	-0.212	0.468	0.174	0.610	0.033	0.918	0.194	0.197
Systolic pressure (mm Hg)	0.288	0.298	-0.296	0.378	-0.115	0.709	-0.011	0.943
Diastolic pressure (mm Hg)	0.080	0.776	-0.523	0.099	-0.192	0.530	0.192	0.197

r: correlation coefficient; *: Correlation is significant at p value ≤ 0.05

Correlation analysis between Estradiol (pg/ml) and some physiological and biochemical parameters in pre and post menopause type 2 diabetic patients and control group.

In both premenopausal and postmenopausal diabetic patients and control group the correlation analysis showed no significant correlation of all parameters with estradiol hormone as shown in table (3).

Table (3) Correlation analysis between Estradiol (pg/ml) and some physiological and biochemical parameters in pre and post menopause type 2 diabetic patients and control group.

Estradiol (pg/ml)								
Parameters	Control group				Diabetic patients			
	Pre menopause		Post menopause		Pre menopause		Post menopause	
	r value	p value	r value	p value	r value	p value	r value	p value
Age	-0.352	0.139	-0.486	0.129	-0.051	0.876	-0.276	0.089
HBA1c	0.256	0.289	-0.263	0.435	-0.061	0.852	-0.121	0.462
FBG (mg/dl)	0.205	0.400	0.074	0.829	0.219	0.494	-0.243	0.137
Insulin (μIU/ml)	0.192	0.461	0.170	0.638	0.071	0.836	0.031	0.855
Insulin Resistance	0.227	0.381	-0.460	0.155	0.103	0.763	-0.028	0.868
Insulin sensitivity	-0.167	0.522	0.004	0.990	-0.050	0.884	-0.193	0.247
Systolic pressure (mm Hg)	0.209	0.391	0.236	0.485	0.230	0.472	0.002	0.988
Diastolic pressure (mm Hg)	0.169	0.488	0.443	0.173	-0.014	0.966	-0.047	0.777

Correlation analysis between Insulin (μIU/ml) and some physiological and biochemical parameters in pre and post menopause type 2 diabetic patients and control group.

In both premenopausal and postmenopausal diabetic patients and control group the correlation analysis showed that there were highly significant negative correlation between Insulin and insulin sensitivity, while highly significant positive correlation with insulin resistance.

In post menopausal diabetic patients, the results of correlation analysis showed that there were significant negative correlation between insulin and HB_{A1c} as shown in table (4).

Table (4) Correlation analysis between Insulin (μIU/ml) and some physiological and biochemical parameters in pre and post menopause type 2 diabetic patients and control group.

Insulin (μIU/ml)								
Parameters	Control group				Diabetic patients			
	Pre menopause		Post menopause		Pre menopause		Post menopause	
	r value	p value	r value	p value	r value	p value	r value	p value
Age	-0.253	0.328	-0.258	0.443	-0.520	0.083	-0.249	0.099
HBA1c	0.232	0.370	-0.009	0.979	0.119	0.713	-0.319	0.033*
FBG (mg/dl)	0.079	0.762	-0.430	0.187	0.545	0.067	-0.093	0.542
Insulin Resistance	0.991	0.000**	0.966	0.000**	0.931	0.000**	0.931	0.000**
Insulin sensitivity	-0.590	0.013*	-0.765	0.006**	-0.871	0.000**	-0.659	0.000**
Systolic pressure (mm Hg)	-0.355	0.162	0.164	0.669	-0.332	0.292	-0.055	0.718
Diastolic pressure (mm Hg)	-0.306	0.232	-0.011	0.975	0.031	0.924	-0.084	0.582

Correlation analysis between HB_{A1c} and some physiological and biochemical parameters in pre and post menopause type 2 diabetic patients and control group.

The results of correlation analysis of premenopausal control group showed highly significant positive correlation between $hemoglobin_{A1c}$ (HB_{A1c}) and fasting blood glucose FBG, while significant inverse correlation with insulin sensitivity.

In premenopausal and postmenopausal diabetic patients groups there were highly significant positive correlation between $hemoglobin_{A1c}$ (HB_{A1c}) and fasting blood glucose (FBG), as shown in table (5).

Table (5) Correlation analysis between Insulin HB_{A1c} and some physiological and biochemical parameters in pre and post menopause type 2 diabetic patients and control group.

HB_{A1c}								
Parameters	Control group				Diabetic patients			
	Pre menopause		Post menopause		Pre menopause		Post menopause	
	r value	p value	r value	p value	r value	p value	r value	p value
Age	-0.163	0.505	-0.140	0.664	0.263	0.386	-0.079	0.596
FBG (mg/dl)	0.590	0.008**	0.452	0.140	0.695	0.008**	0.524	0.000**
Insulin Resistance	0.293	0.254	0.557	0.060	0.432	0.170	-0.183	0.229
Insulin sensitivity	-0.524	0.031*	-0.543	0.068	-0.030	0.927	0.142	0.348
Systolic pressure (mm Hg)	0.023	0.926	0.258	0.419	0.096	0.756	-0.003	0.984
Diastolic pressure (mm Hg)	0.060	0.808	0.357	0.255	0.295	0.327	-0.172	0.247

Discussion

Insulin hormone, Insulin resistance and insulin sensitivity

The results of the present study showed that the patients with type2 diabetes, have significantly higher insulin hormone levels than control group as shown in table (1) and these results are in agreement with the study of [20]. where they found an increase of insulin hormone levels in type2 diabetic patients and this elevation have association with insulin resistance status. Also, [21], explained the role of insulin resistance in the development of hyperinsulinemia with the compensating of pancreas in. producing more insulin and this will lead to development of type 2 diabetes and reported that hyperinsulinemia associated with several risks such as high levels of triglycerides, uric acid, atherosclerosis, hypertension and obesity. An inverse association of insulin resistance with 25(OH)D concentration has been found for 25(OH)D values between 16 and 36 ng/mL [22]. Another study suggested that 25(OH)D possibly modulated glycemic responses, both in impaired glycemia and in healthy subjects [23]. Other studies have indicated a role for vitamin D supplementation in modulation of insulin resistance and improvement of its resultant complications. In Von Hurst et al., insulin resistance was reduced but only if serum25(OH)Don supplementation reached >80nmol/L (>32 ng/mL) [24].

Estradiol hormone

The results of this study demonstrate that Estradiol levels significantly lower in post menopausal females with type 2 diabetes and in control group than pre menopausal females as shown in table (1) and these results are in agreement with [25, 26] who found that in females type 2 diabetes is associated hyper androgenism as a consequence of hypothalamic-pituitary axis alteration. In addition, this alteration in the levels of testosterone in males and females appear to be linked with insulin resistance [27]. In menopause vitamin D deficiency occur due to decrease in Estrogen ,as it increase the activity of the enzyme responsible for activating vitamin D and its receptors (VDRs). In a study in postmenopausal women, fasting glucose levels were found to be negatively correlated with serum 25(OH)D [28]. Current recommendation by National Institute of Health is to maintain vitamin D levels above 50 nmol/l, and post menopausal females should take 600-800 IU/day. By this study we conclude that vitamin D deficiency is higher in diabetes mellitus type 2 patients as it is related to glucose control. Vitamin D deficiency in post menopausal diabetic females was more as compare to pre menopausal females. There is more decline of levels of vitamin D in post menopausal females, due to the effect of decreased levels of estrogen. Levels of vitamin D were significantly decreased in post menopausal phase.

Hemoglobin$_{A1c}$

The hemoglobin A1C test - also called HbA1C, glycated hemoglobin test, orglycohemoglobin - is an important test used to evaluate glycemic control over a period of 3-4 months. In June 2009, the International Expert Committee, which represents several major diabetes groups, recommended using HbA1C to diagnose diabetes [29].The results of this study showed that there were significant elevation ($p \leq 0.05$) of hemoglobin A1c in type 2 diabetic patients than control groups as shown in table (1) Also this study showed an inverse correlation with vitamin D and this with agreement with a study that showed an inverse correlation between vitamin D levels and Hb_{A1c} level [30, 31]. This suggested that keeping vitamin D concentration in the normal range may help in maintaining the glucose homeostasis. Sheth et al. could not establish any association between Vitamin D deficiency and Glycated haemoglobin which is in disagreement with the findings of the present study [32]. In a study done by Athanassiou et al. Vitamin D values were found to be 19.26 ± 0.95 ng/ml in type 2 Diabetes mellitus cases which were in the insufficiency range. The findings of Athanassiou et al. are in agreement with the findings of the present study since the Vitamin D levels of the present study were also in the insufficiency range. In their study, they observed an inverse relationship between Vitamin D levels and Glycated haemoglobin which were in agreement with the findings of the present study [33].

Fasting Blood Glucose (FBG)

The results of this study showed significant elevation of FBG in type 2 diabetic group than control as shown in table (1) and this agreed with the former studies of [34,35]. Hyperglycemia is the main feature of diabetic and its elevation may associated with the elevation of glucagon level which involve in hepatic glucose production ,the major factor that participate in fasting and postprandial hyperglycemia [36]. Other studies indicate that hyperglycemia may result from elevation of cortisol levels which is ensured the elevation of blood glucose levels and in diabetic state it has undesirable role as it tend to sustain hyperglycemia [37,38]. Recent review summarized that although there were inverse associations between 25OHD and IR, the systematic reviews and meta-analysis in that review did not favor a casual role [39]. The present findings are in line with previous observational studies that found an inverse association between 25OHD status and high FPG levels [40,48] and high HbA1c levels [30]. However, these studies adjusted for fewer variables, with smaller sample sizes than our study and were not population based [41,47].

Vitamin D

This study results showed that there were vitamin D insufficiency among diabetic patients and control group as shown in table (1). In menopause vitamin D deficiency occur due to decrease in Estrogen ,as it increase the activity of the enzyme responsible for activating vitamin D and its receptors (VDRs). In a study in postmenopausal women, fasting glucose levels were found to be negatively correlated with serum 25(OH)D [28]. Current recommendation by National Institute of Health is to maintain vitamin D levels above 50 nmol/l, and post menopausal females should take 600-800 IU/day. By this study we conclude that vitamin D deficiency is higher in diabetes mellitus type 2 patients as it is related to glucose control. Vitamin D deficiency in post menopausal diabetic females was more as compare to pre menopausal females. There is more decline of levels of vitamin D in post menopausal females, due to the effect of decreased levels of oestrogen. Levels of vitamin D were significantly decreased in post menopausal phase. Vitamin D deficiency and insufficiency explained by several reasons among them the flat angle of incidence of the sun is responsible for the low intensity of the sun's rays. Germany is located between 47th and 55th parallels, i.e., in the northern hemisphere of the earth, at same level as Canada. This also explains why so many people, especially in the winter months, suffer from vitamin D deficiency [25(OH)D<20 ng/mL or 50 nmol/L]. The UV index can also be used to estimate sun-dependent vitamin D formation in the skin. With a UV index of less than 3, no vitamin D synthesis can take place in the skin [42]. hiamolera et al. observed a 25 hydroxy Vitamin D of 23.4 ± 8.3 ng/ml in patients with type 2 Diabetes mellitus which was higher than the results of the present study [43]. Lakshmi et al. observed a mean 25 hydroxy Vitamin D values of 16.34 ng/ml in cases. The findings of Lakshmi et al. is in close agreement with the 25 hydoxy Vitamin D levels of the present study which was 16.07 ng/ml. Lakshmi et al. observed a significant difference between 25 hydroxy Vitamin D levels between cases and controls which was not observed in the present study [44,49].

References

1. Chen C. *et al.* (2011). Rapid Range Shifts of Species Associated with High Levels of climate warming. *Science.*,333 (6045): 1024-1026.
2. Das, S.K and Elbein, S.C. (2006)The genetic basis of type 2 diabetes. Cellscience.,131-1002.
3. American Diabetes Association (ADA)Statement (2017).Diagnosis and classification of diabetes mellitus .Diabetes Care.,36,67-74.
4. Dasa, M. (2012). Um Novo Guideline e suasImplicações Práticas. Revista InovarSaúde., 17: 12-15.
5. Castro, L.C.G. (2011). O Sistema Endocrinológico Vitamina D. Arquivos Brasileiros de Endocrinologia & Metabologia., 55: 566-575.
6. Schuch, N.J. (2011). Relação entre a Concentraçãosérica da Vitamina D, Polimorfismo no Gene VDR e Sindrome Metabólicaem Indivíduos Adultos. In: EdUSP (São Paulo), Ed., Programa de Pós-graduaçãoem Nutriçãoemsaúde Pública, Faculdadeem Saúde Pública, Universidade de São Paulo, São Paulo-SP., 12-103.
7. Schuch, N.J.; Garcia, V.C. and Martin, L.A. (2009). Vitamina D e doençasendocrinometabólicas. ArquivosBrasileiros de Endocrinologia&Metabologia., 53: 625-633.
8. Lopes, P.M.A. (2014) O Papel da Vitamina D nas Doenças AutoimunesSistêmicas. In: Centro Hospitalar do Porto, Ed., Mestrado Integradoem Medicina, Instituto de Ciênciasbiomédicas Abel Salazar, Universidade do Porto, Porto, 1-16.
9. Kwak, E.K.; Park, H.S. and Kang, N.M. (2014). Menopause knowledge, attitude, symptom and management among midlife employed women. J Menopausal Med., 20: 118-25.
10. Al-Safi, Z.A. and Polotsky, A.J. (2015). Obesity and menopause. Best Pract. Res. Clin. Obstet. Gynaecol., 29: 548–553.
11. Polotsky, H.N. and Polotsky, A.J. (2010). Metabolic implications of menopause. Semin. Reprod. Med., 28: 426–434.

12. Franklin, R.M.; Ploutz-Snyder, L. and Kanaley, J.A. (2009). Longitudinal changes in abdominal fat distribution with menopause. *Metabolism*., 58: 311–315.
13. Fuyong, D.; Virtue, E.; Wang, H. and Xiao-Feng, Y. (2013). Metabolomic analyses for atherosclerosis, diabetes, and obesity. Biomark Res 1: 17-20.
14. Kim, H.Y.and Kong, E.H. (2013). The Association between serum GGT level and bone mineral density in postmenopausal women. Kosin Med J., 28:35-41.
15. Vijayalakshmi, C. (2016). Diabetes and Menopause. Journal of Anesthesia & Critical Care., 6(4): 00233.
16. Dong, J.; Lau, C.W.; Wong, S. and Huang, Y. (2014). Cardiovascular benefits of vitamin D. Sheng Li XueBao., 66: 30-6.
17. Barham, D. and Trinder, P.(1972). Analyst;97-142.
18. Stumvoll, M and Gerich, J (2001) Clinical features of insulin resistance and beta cell dysfunction and the relationship to type 2 diabetes. Clin Lab Med 21: 31–51.
19. Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, Quon MJ. (2000).Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab. 85(7):2402-24010.
20. Mamza,Y.P.; Udoh, A.E. and Etukudo,M.H.(2013).Evaluation of serum cortisol and growth hormone in type 2 diabetic subjects attending University of Maiduguri Teaching Hospital, Nigeria. IOSR Journal of Dental and Medical Science.,7(1):53-57.
21. The global diabetes community.(2015).Hyperinsulinemia, Diabetes.co.uk © 2015 Diabetes Digital Media Ltd - the global diabetes community.
22. Heaney, R. P.; French, C. B. and Nguyen, S. et al. (2013). A novel approach localizes the association of vitamin D status with insulin resistance to one region of the 25-Hydroxyvitamin D continuum. Advances in Nutrition., 4(3): 303–310.
23. Badawi, A.; Sayegh, S.; Sadoun, E.; Al-Thani, M.; Arora, P.; and Haddad, P. S. (2014). Relationship between insulin resistance and plasma vitamin D in adults. Diabetes, Metabolic Syndrome and Obesity: Targets andTherapy., 7: 297–303.
24. Von Hurst, P.R.; Stonehouse, W. and Coad, J. (2010). Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient—a randomised, placebo-controlled trial. Br J Nutr., 103: 549–555.
25. Vicennati ,V, Ceroni, L, Genghini, S, Patton, L, Pagotto, U, and Pasquali, R.(2006). Sex difference in the relationship between the hypothalamic-pituitary-adrenal axis and sex hormones in obesity. Obesity (Silver Spring) 14: 235-243.
26. Anantharaman, P. and Schmidt, RJ. (2007).Sexual function in chronic kidney disease. AdvChronic Kidney Dis 14: 119-125.
27. Grossmann,M; ThomasMC, and Panagiotopoulos S, .(2008). Low testosterone levels are common and associated with insulin resistance in men with diabetes. J Clin Endocrinol Metab;93:1834–1840.
28. Need, A.; O'Loughlin, P.; Horowitz, M. and Nordin, B. (2005). Relationship between fasting serum glucose, age, body mass index and serum 25 hydroxyvitamin D in postmenopausal women. ClinEndocrinol (Oxford)., 62: 738–741
29. Ronald, T.; Ackerman, Y. J. and Cheng, D. F. et al. (2011). Identifying Adults at High risk for Diabetes and Cardiovascular disease using hemoglobin A1c. Am J Prev Med., 40: 101-103.
30. Zoppini, G.; Galletti, A.; Targher, G.; Brangani, C.; Pichiri, I.; Negri, C.; Stoico, V.; Cacciatori, V. and Bonora, E. (2013). Glycated Haemoglobin Is Inversely Related to Serum Vitamin D Levels in Type 2 Diabetic Patients. *PLoS ONE.*, 8(12): 82733.
31. Hutchinson, M.S.; Figenshau, Y.; Njølstad, I.; Schirmer, H. and Jorde, R. (2011). Serum 25-hydroxyvitamin D levels are inversely associated with glycatedhaemoglobin (HbA1c). The Tromsø Study. Scand J Clin Lab Invest., 71: 399–406.
32. Sheth, J.J.; Shah, A.; Sheth, F.J.; Trivedi, S.; Lele, M. and Shah, N. (2015). Does vitamin D play a significant role in type 2 diabetes?. BMC Endocrine Disorders., 15: 1-7.
33. Athanassiou, I.K.; Athanassiou, P.; Gkountouvas, A. and Kaldrymides, P. (2013). Vitamin D and glycemic control in diabetes mellitus type 2. Ther Adv Endocrinol Metab., 4: 122-128.
34. Hamaddi, A.M. (2012). Hormone leptin levels and their relationship with some physiological and biochemical variables of non-insulin dependent diabetes mellitus (Type 2) patients.83 pages.

35. Mohamed,A.H.(2014).Glucagon Like Peptide levels and their relationship with some physiological and biochemical variables of non-insulin dependent diabetes mellitus (Type 2) patients. Thesis /Babylon university /college of science, Department of Biology.143 pages.
36. Lefebvre, P.(2006). Alpha-cell Function in Type 2 Diabetes.US Endocrinology., (1):39-40
37. Orskov, L, Schmitz, O, and Bak, JF.(2001). Skeletal muscle glucose uptake, glycogen synthase activity and GLUT 4 content during hypoglycaemia in type 1 diabetic subjects. Scand J Clin Lab Invest.; 61:371-381.
38. Rosmond, R.(2003). Stress induced disturbances of the HPA axis: a pathway to Type 2 diabetes? Med SciMonit.; 9: 35-39.
39. Soares, M.J.; Pannu, P.K.; Calton, E.K.; Reid, C.M. and Hills, A.P. (2017). Vitamin D status and calcium intake in systemic inflammation, insulin resistance and the metabolic syndrome: an update on current evidence. Trends in Food Sci Technol., 62:79–90.
40. Gagnon, C.; Lu, Z.X.; Magliano, D.J.; Dunstan, D.W.; Shaw, J.E. and Zimmet, P.Z. *et al*. (2012). Low serum 25-hydroxyvitamin D is associated with increased risk of the development of the metabolic syndrome at five years: results from a national, population-based prospective study (The Australian Diabetes, Obesity and Lifestyle Study: AusDiab). *J Clin Endocrinol Metab*., 97(6):1953–1961.
41. Manickam, B.; Neagu, V.; Kukreja, S.C. and Barengolts, E. (2013). Relationship between glycated hemoglobin and circulating 25-hydroxyvitamin D concentration in African American and Caucasian American men. EndocrPract., 19(1):73–80.
42. Gröber, U. and Holick, M.F. (2013). Vitamin D. Die Heilkraft des Sonnenvitamins. 2.Auflage, 304 S., Wissenschaftliche Verlagsgesellschaft, Stuttgart,
43. Chiamolera1, P.S.; Amaral, C.A.; Russo, M.C.D.O.; Netto, G.D.O.; Fernandes, R.A. and Andrade, R.T.D. (2016). Prevalence of Low Levels of Vitamin D in Type 2 Diabetes at the City of Mangueirinha, Parana, Southern Brazil. O J EndocrMetab Dis., 6: 8-12.
44. Lakshmi, G.; Jothimalar, and Santhi, S. (2015). Vitamin D Status in Type 2 Diabetes Mellitus. I J Clinic Biochem Res., 2: 140-142.
45. Al-Terehi1, M. al-kilabi2, L.H., AL –Mamoori1, A., Al-Jboori, M.J. , Al-Saadi1, A H. Zaidan H.K. Some Heavy Metals Concentrations in Tumor Tissue, International Journal of ChemTech Research CODEN (USA): IJCRGG 2016,9, ,03 ,407-411.
46. Al-Terehi1, Haider K. Zaidan, Ayad M.J. AL –Mamoori; Ali Hmood Al-Saadi, IsraaHarjan Effective of different factors on trace elements concentrations in Iraqi lactating mother'smilknternational Journal of Pharm Tech Research,Vol.8, No.10, pp 151-157, 2015.
47. Al-Terehi,Aizhar Hamzih Hasan, Haider J. Muhammed** IsraaHarjan Mohsen. Ali H. Al-Saadi*, Haider K. Zaidan Polymorphisms of Glutathione-S-Transferase M1 and T1 Genes in Breast Cancer Tissue (accept publishing)
48. Al-Terehi, RanaGhaleb, Shaimaa A. Al-Oubaidy2, Ali H. Al-Saadi1, Haider K. Zaidan,(2015) Study TNF-α gene polymorphism in Type 1 Diabetic Patients Using Amplification Refectory Mutation System (ARMS) technique , JCPS Volume 9 Issue 3. 1107-1111.
49. Al-Terehi1, M. Hasan1, A.H, AL-Jboory J M. Al-Saadi1 A. Haider, K Zaidan1, Sawsem J obiad (2016) Haplotype Polymorphisms in Cytokines Genes Using Pcr-Sscp Technique in Iraqi Breast Cancer Patients, Der Pharma Chemica, 2016, 8(22):27-31.

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