Open Journal of Endocrine and Metabolic Diseases, 2016, 6, 102-108
Published Online February 2016 in SciRes. http://www.scirp.org/journal/ojemd
http://dx.doi.org/10.4236/ojemd.2016.62014

The Relationship between Serum 25-Hydroxyvitamin D and Resistin Levels in Saudi Diabetic Patients

Ahmed El-Tahir[1*], Abdulaziz F. AL-Kaabbab[2], Muaawia Ahmed Hamza[1], Abdullah A. Saeed[1], Abdulshakour Abdalla[1], May F. AlMohareb[1], Hana S. Alfaleh[1], Gwiria M. H. Satti[1,3]

[1]Faculty of Medicine, King Fahad Medical City, Ministry of Health, Kingdom of Saudi Arabia
[2]Faculty of Medicine, Al-Imam Mohammed Ibn Saud Islamic University, Kingdom of Saudi Arabia
[3]Faculty of Medicine, University of Khartoum, Sudan
Email: *ahmedeltahirm@yahoo.com

Received 10 January 2016; accepted 26 February 2016; published 29 February 2016

Abstract

Objectives: The aim of this study was to investigate the relationship between the levels of 25-hydroxyvitamin D and the adipokine resistin in Saudi diabetic patients and those at high risk to develop atherosclerotic cardiovascular diseases. Methodology: One hundred and sixty seven subjects were recruited for the cross-sectional study at King Fahad Medical City, Saudi Arabia. Blood samples were analyzed for biochemical parameters. Serum 25-hydroxyvitamin D and resistin levels were measured for all the participants. Result: Fifty six type-1, 55 type-2 diabetic patients and 56 healthy controls were recruited. Serum 25-hydroxyvitamin D level in the control group was 44.21 ± 41.80 µg/ml compared to 50.67 ± 35.60 µg/ml in the diabetic group (P = 0.427) with no significant different between type-2 diabetes mellitus and type-1 diabetes mellitus (P = 0.628). Resistin level in the control group was 14.00 ± 7.39µg/ml compared to 20.21 ± 16.94 µg/ml in the diabetic group (P ≤ 0.01), no significant difference between type-2 diabetes mellitus and type-1 diabetes mellitus (P = 0.817). Resistin in those taking vitamin D supplementation was 21.34 ± 18.27 µg/ml; and in those not taking vitamin D supplementation, it was 17.4 ± 11.19 µg/ml; (P = 0.237). There was significant negative correlation between 25-hydroxyvitamin D and resistin in type-2 diabetes mellitus (P ≤ 0.043) and no significant correlation was found between vitamin 25 (OH) D and resistin level in type-1 diabetes mellitus (P = 0.538). Blood urea and creatinine showed significant positive correlation with vitamin 25 (OH) D in one hand and resistin level on the other hand. Discussion and Conclusions: Several *in vitro* and *in vivo* studies have confirmed that the vitamin 25 (OH) D have numerous important functions in the body. The circulating vitamin 25 (OH) D and re-

*Corresponding author.

How to cite this paper: El-Tahir, A., AL-Kaabbab, A.F., Hamza, M.A., Saeed, A.A., Abdalla, A., AlMohareb, M.F., Alfaleh, H.S. and Satti, G.M.H. (2016) The Relationship between Serum 25-Hydroxyvitamin D and Resistin Levels in Saudi Diabetic Patients. *Open Journal of Endocrine and Metabolic Diseases*, **6**, 102-108. http://dx.doi.org/10.4236/ojemd.2016.62014

sistin levels were associated with general inflammation in renal diseases. This study showed significant negative correlation between resistin level and vitamin 25 (OH) D in type 2 diabetes mellitus reflecting their roles in glucose homeostasis. The positive correlation of resistin and vitamin D with urea may reflect their involvement in kidney dysfunction. The level of serum resistin showed slight increase in diabetic patients compared to control group and it was higher in type-2 diabetes mellitus. More efforts are needed to explore the physiological mechanism of vitamin 25 (OH) D and resistin action in metabolic disorders.

Keywords

25-Hydroxyvitamin D, Resistin, Diabetes Mellitus, Kingdom of Saudi Arabia

1. Introduction

There is growing evidence that vitamin D deficiency can be a contributing factor in the development of both type 1 and type 2 diabetes [1]-[4]. Vitamin D might function as an immune and insulin secretion modulator [5] and had also been shown to down regulate the production of several cytokines in *in vitro* studies [6]. Additionally, vitamin D might also provide protection against major health problems such as autoimmune disease, cardio-metabolic disease, and cancer [7] [8]. It also remains unclear if vitamin D deficiency is associated with insulin resistance and if there is a role for vitamin D replacement in the treatment of glucose intolerance. Hormones such as the adipokines; adiponectin and resistin are a possible link between insulin resistance and adiposity. Furthermore, several clinical and epidemiological studies have revealed positive associations between plasma concentrations of resistin and pro-inflammatory cytokines in diabetics and coronary heart diseases [10]-[12]. Another study done by Vilarrasa [9] in a healthy population showed no significant associations between plasma concentrations of 25 (OH) D and resistin whereas plasma 25 (OH) D showed a negative correlation with body mass index—body fat, waist, hip circumference and with leptin. National surveys in Kingdom of Saudi Arabia (KSA) reported an increasing prevalence of diabetes and obesity affecting more than a quarter of the adult population [13]-[15]. Also in Kingdom of Saudi Arabia, more than 50% of the population suffer from hypovitaminosis D (<50 nmol/l) [16]. To further evaluate whether vitamin D deficiency is associated with diabetes mellitus and changes of adipokine secretion especially resistin, we measured serum 25 (OH) D concentrations and resistin level for Saudi diabetic patients and those at high risk to develop atherosclerotic cardiovascular diseases. Such assessment will predict the individuals at high risk to develop complications, taking into account a comprehensive list of risk factors, including age, obesity and hyperlipidemia.

2. Subjects and Methodology

This study is a cross-sectional, health facilities-based study, conducted in central state, Kingdom of Saudi Arabia during April 2012-September 2013. Patients are diagnosed as type-1 or type-2 Diabetes Mellitus according to the WHO classification (1999) and fulfilling the set criteria for enrollment as exclusion of pregnant women. One hundred and eleven diabetic patients; 52 males and 59 females, were enrolled in the study. Fifty six were recruited as age and sex matched healthy controls. Written consents were obtained and investigations were conducted according to the principles expressed in the Declaration of Helsinki. Blood; 5 ml, was collected from each participant in plain vacutainers and serum was separated after centrifugation and stored at −20˚C till analysis.

Demographic and clinical data of the study groups were collected through a questionnaire filled by patients prior to samples collection. Weight and height of participants were measured and BMI was calculated.

2.1. Laboratory Investigations

Glycated haemoglobin was measured from venous blood samples collected following overnight fast using the chromatographic based method [17]. Triglycerides and high-density lipoprotein cholesterol (HDL-C) were determined by enzymatic methods. 25-hydroxyvitamin D was measured by specific ELISAs in accordance with

the instructions provided by the manufacturer (IDS, Tyne & Wear, UK). Serum resistin on fasting blood was measured using a human resistin Quantikine ELISA kit Cat DRSNOO (R & D Systems, UK) following the manufacturer's protocol.

2.2. Statistical Analysis

Parametric (mean + standard deviation (SD) and nonparametric measurements were calculated using SPSS package version 18 windows. Correlation coefficient and T-test was used and $P \leq 0.05$ was considered as significant.

3. Result

One hundred and eleven diabetics and 56 healthy controls were recruited in this study. The mean age of the diabetic group was (33.29 ± 23.13) and the mean duration of diabetes mellitus was (8.61 ± 7.27) year and the body mass index (BMI) was (27.42 ± 10.1).

Table 1 shows the levels of vitamin 25 (OH) D and resistin in the study group. Serum resistin level in the diabetic group was higher than that of the control group ($P < 0.001$).

Table 2 shows the mean ± standard deviation (SD) of biochemical parameters in diabetic groups. BMI was higher in DM type-2 and lower in DM type-1 compared to the reference values; while glycated haemgolobin was higher than the reference values in the 2 groups. The liver enzymes are in the normal range for the study group. For lipid prolife, only triacyglycerol showed higher result than the reference value in the 2 diabetic groups. Biochemical parameters for kidney function test, creatine is normal while the plasma urea levels are to the upper reference values.

Table 1. The level of vitamin 25 (OH) D and resistin levels in the study group.

Group	Vitamin 25 (OH) D (total) nmol/ml	Resitin µg/ml
Control	44.21 ± 41.80	14.00 ± 7.39
DM	50.67 ± 35.60	20.21 ± 16.94
DM type-1	51.67 ± 36.98	19.44 ± 17.05
DM typ-2	48.41 ± 34.54	21.71 ± 16.52

Table 2. Biochemical parameters in the Study groups (mean ± SD).

Parameters	Control	DM type-2	DM-type-1
Age (year)	30.45 ± 13.5	52.3 ± 17.1	14.6 ± 8.2
Duration of the disease (year)	-	10.4 ± 8.5	7.3 ± 5.9
BMI	28.9 ± 11.9	33.1 ± 10.7	22.12 ± 5.7
HB A1c %	6.1 ± 1.1	8.9 ± 2.0	10.0 ± 1.7
LDH (U/L)	1.86 ± 0.87	2.62 ± 0.77	2.84 ± 0.89
AST (U/L)	-	31.4 ± 58.5	34.0 ± 28.2
ALT (SGPT) (U/L)	33.0 ± 0.0	38.9 ± 13.2	49.0 ± 26.8
Alkaline phosphatase (U/L)	82.0 ± 0.0	104.6 ± 32.0	234 ± 119.2
Triacylglycerol (mmol/L)	0.97 ± 0.04	2.08 ± 1.4	1.84 ± 1.42
Total cholesterol (mmol/L)	3.55 ± 0.49	4.39 ± 0.95	4.46 ± 1.22
LDL cholesterol (mmol/L)	1.86 ± 0.87	2.62 ± 0.77	2.84 ± 0.89
HDL-cholesterol (mmol/L)	1.4 ± 0.07	1.07 ± 0.27	1.17 ± 0.43
TSH mlU/L)	5.09 ± 2.2	3.09 ± 2.7	4.08 ± 5.17
T4 (pmol/L)	15.85 ± 2.2	15.24 ± 2.3	16.18 ± 2.19
Creatinine (µmol/L)	59.0 ± 0.0	83.2 ± 37.8	62.3 ± 22.25
Urea (mmol/L	3.3 ± 0.0	5.87 ± 3.7	4.59 ± 1.9
Calcium (mmol/L)	-	2.33 ± 0.12	2.3 ± 0.118

Table 3 shows vitamin D and resistin levels in diabetic complications. The highest level of resistin was for nephropathy, neuropathy and cardiopathy while the lowest was found in hyperlipidemia. There is significant difference in the resistin level between cardiopathy, nephropathy and retinopathy compared to the healthy control. The level of vitamin 25 (OH) D was also high in patients with hyperlipidemia and neuropathy and the lowest was found in nephropathy, this may explain the role of kidney function on vitamin D levels.

Table 4 shows the level of resistin level and vitamin 25 (OH) D accordingly to the gender, positive family history of diabetes mellitus, statin medication and vitamin 25 (OH) D supplementation. Vitamin 25 (OH) D levels showed genetic link ($P = 0.006$) with positive family history for the first degree relative whereas resistin showed non-significant genetic link ($P = 0.07$). In this study, no significant increase for resistin and vitamin D levels was found with vitamin D supplementation or taking statins; the cholesterol lowering drugs. There is weak correlation between resistin level and hypertension and strong correlation between incidence of hypertension and hyperlipidemia and the use of statin drugs P values ≤ 0.0001.

Table 5 shows the correlation of plasma vitamin 25 (OH) D and resistin with biochemical parameters. There is significant negative correlation between resistin level and vitamin 25 (OH) D in type 2 diabetes mellitus reflecting the roles of vitamin D in type-2 diabetes mellitus (P value 0.043). Vitamin 25 (OH) D level showed significant positive correlation with creatinine and urea (P-values 0.018, 0.036) respectively. Whereas resistin level showed profound, non-significant correlation ($P = 0.078$) with calcium level. All other biochemical parameters including lipid profile were not significantly correlated with plasma resistin or vitamin 25 (OH) D level.

4. Discussion

This cross-sectional study which was intended to explore whether there is a relationship between 25' (OH) vitamin D and serum resistin levels among diabetic patients that might affect the severity of the disease. The study showed that vitamin 25 (OH) D level was at the bottom of the normal range in the control and the diabetic groups. The life style of Saudi subjects such as no sun exposure and the high body fat mass which leads to limited bioavailability of vitamin D caused by the trapping of vitamin D in adipose tissue may further increase the

Table 3. Resistin and vitamin 25 (OH) D levels with diabetic complications.

Complications	Number	Vitamin 25 (OH) D	Resistin
Neuropathy	9	52.72 ± 43.4	26.26 ± 17.59
Nephropathy	14	47.9 ± 25.01	25.16 ± 20.42
Retinopathy	23	50.85 ± 35.01	23.33 ± 16.34
Cardiopathy	22	48.50 ± 37.55	25.44 ± 16.6
Hyperlipidemia	44	54.58 ± 33.00	19.93 ± 33.00
Hypertension	42	51.43 ± 40.1	24.13 ± 20.8

Table 4. Resistin and vitamin 25 (OH) D levels accordingly to gender, family history of diabetes, statin medication and vitamin 25 (OH) D supplementation.

	Vitamin 25 (OH) D	P-value	Resistin level	P-value
Male	48.08 ± 32.31	0.591	19.58 ± 14.9	0.264
Female	51.74 ± 39.6		21.54 ± 18.16	
Positive family history (first degree relative)	41.04 ± 23.11	0.006	20.61 ± 17.68	0.07
Negative family history	66.38 ± 33.23		9.99 ± 5.09	
Taking statin drugs	50.85 ± 32.68	0.638	19.94 ± 15.99	0.2
Not taking statin drugs	47.77 ± 33.01		20.17 ± 17.01	
Vitamin D supplementation	48.83 ± 35.51	0.474	21.34	0.273
Without vitamin 25 (OH) D supplementation	54.15 ± 37.51		17.41	

Table 5. The correlation between vitamin 25 (OH) D and resistin with biochemical parameters in diabetes mellitus type-2 (P-values).

	Vitamin 25 (OH) D		Resistin	
	Diabetes mellitus type-2	Diabetes mellitus type-1	Diabetes mellitus type-2	Diabetes mellitus type-1
HbA1c	0.231	0.113	0.231	0.047*
Total cholesterol	0.79	0.024*	0.797	0.336
LDL-cholesterol	0.77	0.098	0.767	0.559
HDL-cholesterol	0.937	0.937	0.937	0.225
Triacylglycerol	0.412	0.412	0.412	0.984
AST	0.318	0.921	0.318	0.561
ALT	0.202	0.202	0.202	0.569
LDH	0.375	0.407	0.101	0.775
Creatinine	0.018*	0.197	0.018*	0.670
Urea	0.036*	0.036*	0.013*	0.694
Calcium	0.90	0.424	0.943	0.424
Resistin	0.043*	0.538		
Vitamin 25 (OH) D			0.043*	0.538

*P value ≤ 0.05.

risk of vitamin D deficiency. Therefore it is possible that vitamin D deficiency may contribute to insulin resistance and the development of metabolic syndrome secondary to inflammation aggravated by the increased resistin levels in diabetics. Our results revealed that the level of serum resistin slightly increases among diabetic patients compared to the control group ($P \leq 0.061$). Given the obesity-insulin resistance-inflammation link and convergence of adipocyte and macrophage function, resistin may provide unique insight into links between obesity, inflammation, and metabolic syndrome risk in humans. This connection between macrophage derived resistin and adipose tissues may further clarify the understanding of obesity as an inflammatory state and implicates resistin as a potential modulator of that state. Vitamin D has been shown to inhibit antigen-induced T cell proliferation and cytokine production [18], acting as an immune-modulatory agent [19]. Recently, vitamin D has been proposed to also have anti-inflammatory properties. Interestingly, the serum resistin level among patient with type 2 diabetes was found to be higher than those of type 1 and non-diabetic control. Serum resistin level in this study showed to be much higher level in neuropathy and nephropathy compared to the other complications, whereas vitamin 25 (OH) D was slightly increased in hyperlipidemia and neuropathy. Hyperlipidemia showed lower resistin level compared to the other complications. This may reflect the effect of hypolipidemic drugs on circulating resistin in diabetic subjects and slight increase in vitamin 25 (OH) D. Blood urea and creatinine showed significant correlation with the resistin level and vitamin 25 (OH) D, while vitamin 25 (OH) D showed negative correlation with resistin in type-2 diabetes mellitus. The role of low vitamin 25 (OH) D and increased resistin as pro-inflammatory may affect the kidneys dysfunction. Thus circulating vitamin 25 (OH) D and resistin levels were associated with general inflammation, and renal disease. Our findings do not fully support the hypothesis that vitamin D deficiency is associated with poorer glycemic control which can be caused by β-cell dysfunction as well as insulin resistance as there was no correlation between HB A1c and vitamin D level ($P = 0.874$). On the other hand the effect of vitamin D on diabetes might be mediated through the increased serum resistin level at decreased levels of vitamin 25 (OH) D as seen in type-2 diabetes mellitus through negative correlation between resistin and vitamin D in the present study. This effect would be influenced by obesity while such correlation was not detected in type-1 diabetes mellitus or non-diabetic study group.

5. Conclusion

This study showed significant negative correlation between vitamin 25 (OH) D and resistin level in type-2 di-

abetes mellitus. The correlation of vitamin D and resistin with urea may reflect their involvement in kidney dysfunction and the circulating vitamin 25 (OH) D and resistin levels are associated with general inflammation in renal diseases. The level of serum resistin showed slight increase in diabetic patients compared to control group and it was higher in type-2 diabetes mellitus. More efforts are needed to explore the physiological mechanism of vitamin 25 (OH) D and resistin action in metabolic disorders.

6. Recommendations

To investigate the impact of vitamin D treatment in diabetic and the role of vitamin D on glucose homeostasis and resistin as an inflammatory marker, future studies should use highly sensitive measures of insulin sensitivity and β-cell serum markers as well as other inflammatory markers.

7. Limitations

The cross-sectional nature of the study and the small sample size limits the findings of the study. Several major confounders were also not included including season which has a counterintuitive effect in the vitamin D status of citizens residing in the Gulf region [20].

Ethical Consideration

The project was reviewed and approved by the Institutional Review board-IRP King Fahad Medical City, Log number 11-040. All patients were consented before their enrollment in the study.

Acknowledgements

This study was funded by SRC, Faculty of Medicine, King Fahad Medical City under grant no.10/32/1.

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