RELATIONSHIP BETWEEN C PEPTIDE AND CHRONIC COMPLICATIONS IN YEMENI TYPE-2 DIABETIC PATIENTS.

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ABSTRACT

Objectives; The relationship between post prandial c-peptide level and micro vascular and macro vascular complications is poorly known in type 2 diabetes .The aim of the study was to explore the relationship between the level of C- peptide and the diabetic micro vascular and macro vascular complication in Yemeni type 2 diabetic patients **Methods ;** One hundred seventy type 2 diabetic patients 93 (65%) male and 77 (53.9%) female aged more than 30 years were recruited from Al-Kuwait University Hospital and consultation clinic and studied cross section ally .They undergo complete clinical examination included assessment for the presence of both micro vascular (diabetic retinopathy ,sensory peripheral neuropathy and nephropathy) and macro vascular (IHD , ischemic stroke , peripheral vascular diseases) complication were determined subjectively by experienced physician , and the following laboratory investigation (HbA1C , lipid profile , and post prandial serum C-peptide level)**Results ;** Onehundred seventy type 2 diabetic patients included in this study 93 (65%) was male and 77 (53.9%) was female , of all studied type 2 diabetic patients 54 (31.7%) had low serum C-peptide level and 116 (68.2%) had normal or high serum post prandial C- peptide level ; those with low serum C-peptide level had statistically significant high prevalence of diabetic nephropathy 61.1%, retinopathy 55.5% and sensory peripheral neuropathy 74%) versus those with high or normalserum C-peptide level(12.9%, 16.3% and 19.8% respectively) =P-value ≤ 0.05 , while there is no significant difference between those with low and high or normal serum C-peptide regarding macro vascular complication (ischemic stroke and peripheral vascular diseases) except for ischemic heart diseases .**Conclusion ;**The result of this present study showed that type 2 diabetic patients with low serum C- peptide level has high prevalence of diabetic micro vascular complication than those with normal or high level

Key words ;

C-peptide , diabetic complication , nephropathy , peripheral neuropathy , retinopathy

INTRODUCTION

Proinsulin and C-peptide was first described in 1967 in connection with the discovery of the insulin biosynthesis pathway.(1) It serves as a linker between the A- and the B- chains of insulin and facilitates the efficient assembly, folding, and processing of insulin in the endoplasmic reticulum. Equimolar amounts of C-peptide and insulin are then stored in secretory granules of the pancreatic beta cells and both are eventually released to the portal circulation. Initially, the sole interest in C-peptide was as a marker of insulin secretion and has as such been of great value in furthering the understanding of the pathophysiology of type 1 and type 2 diabetes. C-peptide has long been considered to be a biologically inert portion of proinsulin. More recently, C-peptide has been found to bind to endothelial cells, renal tubular cells and fibroblasts in a stereospecific manner and to stimulate Na-K-ATPase, endothelial nitric oxide synthase activities and nuclear factor-kB activation in endothelial cells exposed to hyperglycemia (1, 2).C -peptide is by now identified as a biologically active substance. Many studies initiate C-peptide as an active peptide hormone with important physiological effects, which affects renal, neuronal, and micro vascular functions in patients with diabetes (3,4). The relation between C-peptide levels and the micro vascular and macro vascular complications of type 2 diabetes is unclear. Some studies find that residual insulin secretion has a protective effect against these complications, while others do not. Lower C-peptide levels have been associated with the presence of retinopathy (5), with the progression of diabetic microangiopathies (such as retinopathy and nephropathy) (6), with increasing albuminuria, and with the duration of diabetes (7). On the other hand, higher C-peptide concentrations have been associated with parasympathetic neuropathy (8), coronary artery disease, peripheral vascular disease, and autonomic neuropathy (9). Still other studies report no relation between C peptide levels and sensorial neuropathy, nephropathy, or retinopathy (9, 10, 11).

C-peptide increases capillary blood flow in type 1 diabetic patients (12), through increased influx of Ca2+ into endothelial cells, which facilitate release of NO from the endothelium. Many studies have demonstrated beneficial effects of C-peptide on the long-term complications in type 1 diabetic patients. This could have an important therapeutic implication (13, 14). For example, decreased blood flow in the extremities might be prevented by C-peptide (15). Moreover, improvements of endo neural blood flow and axonal swelling have been also demonstrated by introduction of C-peptide (16). In numerous studies of type 1 diabetes glomerular hyper filtration, hypertrophy, and proteinuria have been reduced by C-peptide (16, 17, 18). C-peptide treatment improves sensory nerve function in early stage of type 1 diabetic neuropathy (19). The effects of C-peptide on type 2 diabetes as well as on the cell proliferation and apoptosis are very controversial at present. Levels of inflammation in type 1 and type 2 diabetes are still unknown, but it has been found that plasma levels of IL-6 correlate with C-peptide levels and insulin sensitivity (20). The metabolic syndrome, prediabetes, and type 2 diabetes mellitus accelerate vascular disease and increase development of the disease (21). At the moment the reasons for the increased predisposition and progression of atherosclerosis in patients with diabetes are unknown. In vivo model from Vasic et al.(22) showed increased deposition of C-peptide in early atherosclerotic lesions in ApoE-deficient mice. C-peptide deposition was followed by recruitment of inflammatory cells

into the vessel wall and increased infiltration of monocytes/macrophages as well as increased proliferation of smooth muscle cells. These results are also in agreement with in vitro data of Swiss 3T3 fibroblasts, where C-peptide has been shown to activate PI-3 kinase (23) as well as increased expression of PPAR-γ regulated CD36 scavenger receptor in human THP-1 monocytes by C-peptide. These results recommend that C-peptide in addition to these effects might promote the differentiation of monocyte/macrophages into foam cells (24). this study showed no differences in E-selectin and ICAM-1 levels as well as levels of the inflammatory markers such as TNFa and soluble IL-6. An explanation could be that C-peptide was used in this model on top of the hypercholesterinemic diet. But these data are in contrast to several findings in which C-peptide has anti-inflammatory effects and reduced up regulation of cell adhesion molecules under inflammatory conditions (25, 26). In mice with endotoxic shock, C-peptide treatment improved survival rate and reduced plasma levels of tumor necrosis factor-alpha (TNFa), macrophage inflammatory protein-1 alpha, and monocyte chemo attractant protein-1 (27).

Methods ;

The study population was type 2- diabetic patients defined according to ADA 2011 (28) who attended the medical clinic of AL-Kuwait University Hospital (KUH) in Sana'a City, Yemen during the study period between the 4th of March 2017 to the 1st of January 2018.

Exclusion criteria

- Type 1- DM
- Any one of the participants who suffered from any of the following conditions that increase the urinary albumin excretion such as urinary tract infection ,hematuria ,acute febrile illness, vigorous exercise, uncontrolled hypertension and heart failure (29).

All subjects were interviewed about their age, habits, occupation, and past history of diabetes and hypertension, as well as their drug intake. Subjects underwent a physical examination consisting of the determination BMI and systolic and diastolic blood pressure. . Height was measured without shoes, and weight was recorded while wearing indoor clothing. Body mass index (BMI) (weight in Kg, divided by height in meters squared) was calculated. The WHO (2012) classification for BMI was used to estimate the degree of obesity (30).

Blood pressure was recorded with the same mercury manometer in the sitting position after 10 – 15 minutes rest. Each subject had two measurements of blood pressureat 5 minutes intervals**.**

Diabetic complication of the participant**were** evaluated subjectively by experienced physician or by referring to their respective medical record

Retinopathy: Patients with bilateral cataracts were excluded for retinopathy. Retinopathy assessed by direct ophthalmoscope that was done after pupillary dilatation by tropicamide 1% eye drops was defined as the presence of at least one micro aneurysm or hemorrhage or exudates in either of the eye (31)***:***

Peripheral sensory neuropathy ; Neuropathy was diagnosed by history of numbness, paraesthesias, tingling sensations, burning sensation and confirmed by touch sensation using 10gm monofilament, vibration sense by tuning fork (128 Hz) and ankle reflex. Painful peripheral neuropathy was diagnosed by history of pain worsening at night

Diabetic nephropathy was evaluated by measuring urinary albumin concentration

Venous blood sampling was performed in the morning after an overnight fast for determination of plasma glucose, triglyceride, High Density Lipoprotein (HDL) cholesterol ,LDL cholesterol (LDL) and serum creatinine . Laboratory techniques for biochemical analysis were glucose oxides for blood glucose, and the enzymatic method for triglyceride , HDL cholesterol and LDL cholesterol. Urinary albumin and creatinine levels were determined in a random spot urine specimen (Tina-Quant, Roche Diagnostics for the measurement of urinary albumin and creatinine). Serum creatinine was determined using a KREA Flex, Dade-Behring, for the measurement of urinary modified Jaffe test (KREA Flex, Dade-Behring),

Serum C-peptide levels was measured by by human C-peptide ELA kit with detection range of 1.3-3.4

Target definitions;
Type 2- diabetes mellitus was defined according to the American Diabetes Association (28) A1C ≥ 6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay. or FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h. In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing . Or 2-h plasma glucose ≥200 mg/dl (11.1mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing. Or In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose _200 mg/dl (11.1mmol | l) , Obesity was defined according WHO definition based on estimation of BMI (30) which is defined as a person's weight (in kilograms) divided by the square of his or her height (in metres). A person with a BMI of 30 or more is generally considered obese. A person with a BMI equal to or more than 25 is considered overweight .
Hypertension was defined according to the European Society of Hypertension-European Society of Cardiology(13,14) as blood pressure ≥ 130/85 mmHg. Dyslipidemia was defined according to the Joint National Committee VII (32) as the following , ≥ 150 mg |dl for TG ,≥100 mg/dl for LDL cholesterol, ≥ 200mg/dl for total cholesterol, and ≥ 45mg/dl (men) and ≥ 55 mg/dl (women) for HDL cholesterol.
Micro albuminuria was defined as an albumin-creatinine ratio of 30 to 300 mg/g, and macro albuminuria as an albumin-creatinine ratio of more than 300mg/g.(33) The research protocol was reviewed and approved by the Ethical Committee of the Faculty of Medicine and Health Sciences, Sana'a University. All participants provided informed consent after explaining the study objectives and that the data will be used only for purpose of the research. Health education both verbally and using education materials was provided to all participants and those who were found to have any medical problem were referred to the specialized clinic for proper management and follow up.

Statistical analysis was under taken using the statistical package for the social sciences (windows version 13.0; SPSS, Chicago IL USA).

Differences between groups were tested statistically using the chi square test for categorical and T test for numerical variables. Data were considered statistically significant when the p-value was ≤ 0.05.

Results ;

This study comprised of 170 type 2 diabetic patients 65.1 % male and53.9 % female with age range of 30-80 (mean 62.05 ± o.24) and diseases duration 2-42 years .

The studied patients was subdivided into two groups , those with low serum C- peptide and those with normal or high serum C-peptide ;

Table 1 shows the prevalence of clinical and laboratory characteristics of both groups ; there was no statistically significant difference between patient with low serum C- peptide level and those with normal or high level regarding body mass index (BMI) , systolic and diastolic blood pressure , HbA1C ,high serum triglyceride(TG)and low serum high density lipoprotein (HDL) . there was only significant difference between both group regarding the duration of DM

Table 1 clinical and laboratory characteristics of type 2 diabetic patients with low and high serum C-peptide leve

Factors	Total =170	Low C-peptide≤1.1=54(31.7%)	Normal or high C-peptide≥1.1=116(68.2%)	p- value ≤ 0.05
Age	56.1±32	53.3±21	49.3±11	0.53
Male gender	93(54.7%)	30(55.5%)	65(56%)	0.2
Duration of DM	10.6±32	9.8±54	11.6±32	0.001
BMI	61(35%)	18(33%)	43(37%)	0.87
BP mmHg	77(45%)	25(46%)	52(44%)	0.5
HbA1C	107(62%)	35(64%)	72(62%)	0.89
Serum TG mg/dl	62(36%)	23(42%)	39(33%)	0.52
Serum HDL ≥ 45 mg/dl in male ≥55mg/dl in female	66(38.8%)	23(42%)	43(37%)	0.64

Table 2 . prevalence of chronic complication in type 2 diabetic patients with low and normal or high serum C-peptide

Factors	Total =170	Low C-peptide=54	High or normal C-peptide=146	-value ≤ 0.05
DNP	48(28.2%)	33(61.1%)	15(12.9%)	0.001
DR	49(28.8%)	30(55.5%)	19(16.3%)	0.0004
SPN	63(37%)	40(74%)	23(19.8%)	0.001
IHD	30(17.6%)	17 (31.4%)	13 (8.9%)	0.01
Stroke	13 (7.6%)	7 (12.9%)	6(4.1%)	0.12
PVD	9 (5.2%)	6 (11.1%)	3 (2%)	0.06

The ischemic heart diseases(IHD) in patient with low serum C- peptide level 31.4% VS those with high or normal post prandial C-peptide level

Diabetic complications are the result of secondary systemic damagecaused by chronic hyperglycemia, and they are a substantial cause ofdiabetes-related morbidity and mortality(18).The therapeutic management of hyperglycemia is the primary intervention for preventing diabetic complications, which is generally achieved by regular insulinsupplement therapy in T1DM, treatment with oral hypoglycemic agents

prevalence of both micro vascular and macro vascular complication in type 2 diabetic with low and with normal or high serum C- peptide level was showed in table 2 ;

Type 2 diabetic patients with low serum C- peptide level has higher prevalence of sensory peripheral neuropathy (SPN) (74%) , diabetic nephropathy (DNP) (61.1%) anddiabetic retinopathy , DR (55.5%) than those with normal or high serum C- peptide , SPN (19.8%) , DNP (12.9%) and DR (16.3%) respectively , p-value ≤ 0.005

Regarding macro vascular complication there was only higher prevalent of

between type 2 diabetic patient with low and normal or high C-peptide level regarding age, BMI, BP,HbA1C, serum TG and HDL .but there was significant correlation between both groups regarding the duration of DM (34, 35)

Regarding micro vascular and macro vascular complication. Type 2 diabetic patients with low serum post prandial C-peptide hormone had higher prevalence of DSPN (74%) , DNP (61.1%) , DR (55.1%) than those with normal or high C-peptide hormone (19.8%, 16.3% and 12.9%) respectively . the finding of the present study showed that the most prevalent diabetic complication in those with low serum C- peptide level is sensory peripheral neuropathy followed by diabetic nephropathy and retinopathy , this is supported by the results from previous studies carried out by Adam K,M (36) , Yeon K,B (37) , Bo etal (38) , and Shen J (35) and Hye, Jin (39)

Other studies showed that there is no relationship between C- peptide level and chronic micro vascular complication of type 2 diabetic patients (39 , 9,10,11)

Regarding macro vascular complication there was only significant correlation between those with low serum c- peptide level and normal or high level only in IHD , which supported by other study (39,40).

Conclusion ;

type 2 diabetic in this study with low postprandial serum C-peptide level was associated with statistically significant increase in the prevalence of micro vascular complication (SPN , DR , DNP) ; in early T2DM, and administration of insulin along with oral hypoglycemic agents in late-stage T2DM. To date, efforts against glycemic control alone have not been entirely successful in preventinglong-term diabetic complications, and alternative therapeutic strategiestargeting aetiological factors for diabetic complication pathogenesis arerequired to prevent organ-specific damage.(19–24). Although two majorfactors (insulin deficiency and subsequent hyperglycemia) contributeto the development of diabetic complications, C-peptide deficiency issuggested to be the third major factor because of beneficial effects of C-peptide against diabetic complications.(3,6–8,10,12–14,19,)vasculopathy is a defect inblood vessels caused by hyperglycaemia, and it leads to organ-specificcomplications. Two major classes of organ-specific diseases caused bydiabetic vasculopathy are micro vascularcomplications, including retinopathy, nephropathy, and neuropathy, and macro vascular complications, including cardiovascular diseases such as myocardial infarctionand cerebrovascular disease manifesting as stroke.(11,18).according to our knowledge there is little data about the rule of C-peptide hormone in the progression of chronic complication of type 2 diabetes , so we decide to do this research to know the relationship between post prandial C-peptide level and chronic complication of type 2 diabetic patients .

This study showed that there was no statistically significant correlation

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prospective and large study will be needed to clarify the association between post prandial serum C-peptide level and chronic micro vascular and macro vascular complication of type 2 diabetes which may be used to reduce the prevalence of this complication

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