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Original Research Article

Insulin resistance status and its relation to plasma uric acid levels in type-2 Diabetes mellitus

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Abstract

Insulin resistance is principle etiological factor for development and progression of type-2 diabetes mellitus and decreased insulin functional at cellular level leads to dyslipidemia which is significant cardiovascular risk factor. Apart from disturbances in glucose and lipid turnover it is claimed that uric acid is altered in type-2 diabetes mellitus, particularly leading to elevations in plasma uric acid levels, suggesting possible relationship among insulin resistance, diabetic dyslipidemia, uric acid levels and cardiovascular risk in type-2 diabetic patients. A study was planned to establish the relationship of plasma uric acid levels to insulin resistance thereby to assess its utility in identifying cardiovascular risk. Type-2 diabetic patients attending OPD of Subbaiah Institute of Medical Sciences and its affiliated hospitals, Shivamogga, in age group of 30-55 years were randomly selected(n=90). Age matched normal controls were taken from employees of Institute and Hospitals (n=90). Diabetic patients were into three groups based on their insulin resistance. Group-1 had insulin resistance between 2-3.5, Group-2 between 3.6-6 and Group-3 had insulin resistance level above 6.1. Fasting plasma levels of glucose, triacylglycerols, HDL cholesterol and uric acid were estimated. The insulin resistance was calculated using ratio of Triacylglycerols/HDL cholesterol. Results shows proportional raise in plasma uric acid levels in diabetic subjects in comparison to insulin resistance indicating plasma uric acid is a measure of insulin resistance in these patients. It can be concluded from present study that plasma uric acid estimation, a cost effective test, is clinically useful in ascertaining insulin resistance hence cardiovascular risk in type-2 diabetic patients.

Keywords: Type-2 Diabetes Mellitus, Insulin Resistance, Cardiovascular risk and Uric Acid.

1. Introduction

Type 2 diabetes mellitus (T2DM) is the most common endocrine disorder in humans. According to the International Diabetes Federation (IDF), currently it affects more than 387 million people worldwide, and by the year 2035, potentially it will affect more than 592 million[1].

T2DM is a chronic-degenerative disorder characterized by the presence of insulin resistance (IR), a condition where a diminished or impaired biological and physiological responses to insulin in tissues, which leads to cluster of abnormalities with serious clinical complications, the most important being cardiovascular disease (CVD)[2]. At the molecular level IR is the consequence of insulin signaling alterations owing to changes in post translational modifications of its receptor or downstream located effecter proteins.[3] IR is normally associated with decreased high density lipoprotein cholesterol (HDLC) levels [4,5]which is a significant CVD risk factor and due to lack of insulin action an increased free fatty acids influx resulting in the over production of Triacylglycerols and LDL which leads to dyslipidemia another major risk factor for CVD. The diabetes induced dyslipidemia with raised IR makes the diabetic population more prone and vulnerable to CVD.

Uric acid(UA), the end product of purine catabolism in humans, has been claimed to be elevated in diabetes mellitus(DM)[6-15], in diabetic complications[16-17] as well as been suggested as a marker of pre-diabetic conditions[18]. The raise in plasma urate levels in DM

have been claimed due to raised purine catabolism either to regulate tissue adenosine levels as adenosine concentration modulates total glucose output [16] or the small amount of H_2O_2 produced during uric acid formation may enhance the insulin effects through modulating thiol enzymes, Protein Tyrosine Phosphatases (PTP's)[19-21]. There are no reports regarding plasma UA levels in comparison to IR status in T2DM patients.

As dyslipidemia is the principle consequence for increased uric acid levels which is commonly observed in T2DM patients may be related to IR another common finding of T2DM, hence a study was undertaken to evaluate the plasma UA levels and to compare the results with IR status, so as to establish the clinical utility of plasma UA levels in the early assessment of CVD risk in T2DM patients.

2. Materials and Methods

Type 2 diabetic subjects attending medical Out Patient Department (OPD) of Subbaiah Institute of Medical Sciences and its affiliated hospitals, Shivamogga, in the age group of 30-55years were randomly selected. Diabetic patients with arthritis, with neuro psychatric disorders, with proved cardiovascular complications and those who are receiving hormone therapy were excluded from the study.

Normal control subjects in the age group of 30-55years were taken from the employees of Subbaiah Institute of Medical Sciences, Subbaiah Institute of Dental Sciences and their affiliated hospitals, Shivamogga. A fasting heparinised blood sample (5-6ml) was collected from the diabetic patients as well as normal control subjects after obtaining an informed consent(IC) from them. These samples were centrifuged at 3000rpm for 6-8 mins and the separated plasma was employed for the estimation of fasting plasma glucose (FPG) [22], uric acid (UA) [23], triacylglyerols(TAG)[24] and high density lipoprotein cholesterol(HDLC) [25]. The study was conducted during September 2017 to May 2018 and was carried out in Central Research Lab, Subbaiah Institute of Medical Sciences, Shivamogga.

The Evaluation of Insulin resistance (IR) is a complex procedure and many methods are available to assess IR and the method employing fasting ratio of plasma Triacylglycerol to plasma HDLC [26-27] was used in the present study.

Insulin Resistance (IR) = fasting plasma TAG/ fasting plasma HDLC

2.1 Statistical analysis

The data obtained were expressed as their Mean ± SD and the statistical significance was calculated using GraphPad-InStat (Version-3.10). $p<0.05$ was considered as significant.

3. Results

The present study includes a total number of 180 subjects which includes 90 normal control subjects and 90 T2DM patients. The T2DM patients were sub grouped into three groups based on their IR status as follows.

	Insulin resistance
Group-1 (n=30)	2-3.5
Group-2 (n=30)	3.6-6
Group-3 (n=30)	>6.1

Results obtained in the present study are narrated in Table-1, Table-2 and Figure-1. Table-1 gives the plasma levels of FPG, TAG, HDLC, UA as well as IR status in normal control subjects and in T2DM patients. It is evident from the table that there is significant elevation seen in the levels of FPG ($p<0.001$), TAG ($p<0.001$), UA ($p<0.001$) and in IR status ($p<0.001$) where as a significant decrease is seen HDLC levels ($p<0.001$) in T2DM patients as compared normal control subjects.

Table-2 narrates FPG and UA levels in IR based subgroups of T2DM patients – Group-1, Group-2 and Group-3. It clear from the table that there is a steady raise in UA levels in Group-1, Group-2 and Group-3 T2DM patients indicating a close relationship between the IR status and UA levels in T2DM patients.

In order to establish the direct correlation of UA levels to IR status in T2DM patients the UA levels are correlated with IR status of T2DM patients and are depicted in Figure-1. As seen from the bar graph in Figure-1 its clear that UA levels are in direct proportionality with IR status in T2DM patients and gives clear indication of IR status in T2DM patients.

Table 1: Showing fasting plasma glucose level (FPG), triacylglycerol(TAG), HDL Cholesterol (HDLC), Uric Acid and Insulin resistance (IR) status in normal control subjects and in Type-2 diabetic patients.

	FPG (mg/dl)	TAG (mg/dl)	HDLC (mg/dl)	Uric acid (mg/dl)	IR
Normal Controls (90)	98.86 ± 18.60	109.90 ± 22.10	48.50 ± 11.20	2.14 ± 0.60	1.90 ± 0.20
Diabetic patients (90)	195.90 ± 22.50***	222.10 ± 21.20***	42.10 ± 8.60***	8.70 ± 0.80***	4.95 ± 1.95***

Note:

1) Values are expressed in Mean ± SD.
2) Number in parenthesis indicates number of subjects.
3) Significance *p<0.05, **p<0.01 and ***p<0.001.

Table 2: Showing the levels of FPG, uric acid (UA) in Group-1, Group-2, and in Group-3 in T2DM patients

	FPG (mg/dl)	UA (mg/dl)
Group-1 (30)	180.70±18.50	4.55±0.60
Group-2 (30)	182.26±16.50	7.66±0.80$^{@@@}$
Group-3 (30)	223.76±21.20***	9.13±1.10***

Note:

1) Values are expressed in Mean ± SD.
2) Number in parenthesis indicates number of subjects.
3) Significance */$^{@}$p<0.05, **/$^{@@}$ p<0.01 and ***/$^{@@@}$p<0.001. @- in comparison to Group-1 and *- in comparison to Group-2.

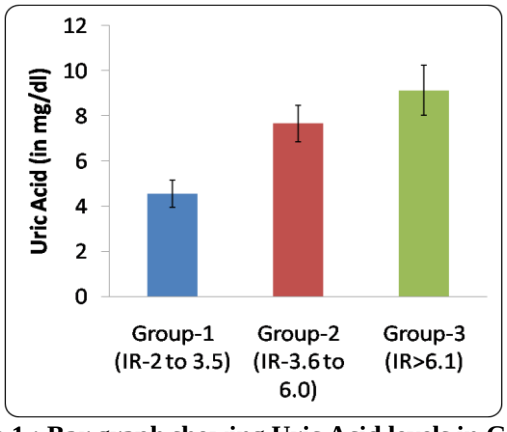

Figure 1 : Bar graph showing Uric Acid levels in Group-1, Group-2 and in Group-3 Diabetic patients.

3. Discussion

Insulin is a major metabolism regulating hormone secreted by β-cells of Islets of Langerhans of the pancreas. The major function of insulin is to counter the concerted actions of a number of hyperglycemia generating hormones and to maintain a low blood glucose level. In addition to its role in regulating glucose metabolism, insulin stimulates lipogenesis, diminishes lipolysis and increases amino acid transport into cells. IR is the inability of insulin to produce its common biological effects at a concentration that is efficient in healthy individuals [28]. IR is principally implicated in the etiology and progression of T2DM apart from other complications like metabolic syndrome. Metabolically and clinically the most detrimental effects of IR are due to disruption in insulin mediated control of glucose and lipid homeostasis in the insulin responsive tissues- liver, skeletal muscle and adipose tissue. IR is characteristic feature associated with T2DM as well as a hall mark feature of metabolic syndrome. The most prevalent cause for IR development is hyperlipidemia or dyslipidemia commonly observed in DM.

The results obtained in the present study in T2DM patients shows a significant raise in plasma TAG and significant decrease in plasma HDLC levels which is in agreement with earlier reports [4,5,29] and establishes T2DM patients with IR do exhibit dyslipidemia[30]. UA levels are primarily altered in T2DM and its elevation is proportionately related to diabetic dyslipidemia[29], and this diabetes-induced-dyslipidemia in principle causes development of IR.. Hyperuricemia which is a component of insulin resistant syndrome[30,31] and also normally observed in T2DM patients is a significant risk indicator of CVD[32-36]. The mechanisms by which raised UA levels may cause CVD do include enhanced platelet aggregation, increased blood viscosity and enhanced propensity to coagulation [37-38].

To establish the relationship between IR and plasma UA levels the T2DM patients were grouped into three groups based on their IR status as Group-1(IR 2-3.5), Group-2 (IR 3.6-6) and Group-3 IR>6.1). It is evident from the table-2 that plasma UA levels are proportionately increased with IR status in T2DM patients(Group-1, Group-2 and Group-3) suggesting plasma UA levels may be an useful index in assessing the IR status. Further it is evident from the graph shown in figure -1 that the raise in plasma UA levels is directly proportional to the IR in T2DM subjects and can be employed to assess the IR status.

The estimation plasma UA levels is quite cost effective and less laborious as compared to more elaborative procedures of assessing IR status hence estimation plasma UA levels are beneficial and economic is assessment of CVD risk in T2DM patients.

4. Conclusion

It can be concluded from the present study that plasma UA levels show a proportional raise compared to IR status in T2DM patients their by may serve as a better risk indicator of IR status in T2DM patients thus facilitates for early detection of onset of CVD.

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