EVALUATION OF BIOCHEMICAL PARAMETERS ASSOCIATED WITH INSULIN RESISTANCE IN TYPE-II DIABETES MELLITUS CASES OF KADAPA AREA

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ABSTRACT:

BACKGROUND: Diabetes mellitus is a chronic disorder that is associated with cardiovascular complications, renal dysfunction and various types of diseases including metabolic syndrome. The present study aimed to investigate the key biochemical parameters such as serum uric acid, vitamin D, vitamin C, magnesium and calcium along with lipid profile that are associated with insulin resistance in type-II diabetes mellitus (DM) patients in Kadapa area.

MATERIAL AND METHODS: The present case-control study was conducted at Fathima Medical College, Kadapa. We recruited 100 type-II diabetic patients and 100 healthy volunteers in the present study. The age groups of the study subjects were between 40 and 70 years in Kadapa urban area. Five ml of fasting blood samples and 3 ml of whole blood samples were collected in the clinical biochemistry laboratory for the estimation of fasting blood sugar (FBS), 2-hour postprandial blood sugar (PPBS) by GOD-POD method along with serum uric acid, magnesium and calcium by IFCC approved fully automated clinical chemistry analyzer. Lipid profile namely total cholesterol, triglycerides, HDL, LDL and VLDL were estimated by the CHOD-PAP and GPO methods. Serum levels of vitamin C vitamin D were estimated by 2.4 dinitrophenyl hydrazine method and CMIA method, respectively.

RESULTS: Our findings indicate that FBS, PPBS and uric acid were significantly elevated ($p<0.001$) in the type-II DM patients when compared to the healthy controls in Kadapa urban area. Conversely, serum magnesium, calcium and vitamin D were significantly lowered in patients with type-II DM as compared with healthy controls. Vitamin C was also significantly reduced ($p<0.0015$) in the type-II DM patients than healthy controls. As there is a strong correlation between diabetes and hypercholesterolemia, we estimated the lipid profile in the present study. In line with the fact, the serum lipid profile namely cholesterol, triglycerides and LDL were significantly higher along with a significant reduction in HDL levels in the type-II DM patients when compared to healthy controls of Kadapa area.

CONCLUSION: In conclusion, the study documents that type-II DM patients in Kadapa area are associated with hypercholesterolemia and lowered vitamin C and D levels. Moreover, since vitamin C shares a structural similarity with glucose, it competes for the glucose transporter and affects the insulin secretion, thus enhancing the severity of DM in the patients of Kadapa population.

KEYWORDS: Uric acid, lipid profile, Vitamin D, Vitamin C, Magnesium, Calcium, type-II diabetes mellitus.

INTRODUCTION

Type-II diabetes mellitus (DM) is a complex, heterogeneous and polygenic metabolic disorder. It is unable to provide adequate insulin secretion, which is characterized by normal glucose homeostasis (Hupfeld et al., 2010). It is the leading form of diabetes, accounting for 90% worldwide, and represents an international fitness crisis. World Health Organization (WHO) predicts a prevalence of 300 million cases with DM by 2025 (Buse et al., 2007). According to the International Diabetes Federation (IDF), number of diabetics in India may increase from 40.9 million to 69.9 million by 2025. Type-II DM describes insulin resistance in peripheral tissues collectively with impaired secretion of insulin (Mohan et al., 2007).

The pathogenesis of type-II DM is characterized by various factors such as resistance to the activity of insulin in peripheral tissues especially in muscle and fat in addition to the liver, irregular insulin secretion, especially in reaction to a glucose stimulus and high levels of glucose produced in the liver. Glucose itself is an important part of cellular ion homeostasis, growing intracellular calcium and reducing intracellular magnesium (Hussain et al., 2009). The prevalence of hypomagnesemia in DM is around 65%. (Shaikh et al., 2011).

Uric acid is the major metabolic breakdown of purine nucleotides, and it is a major component of urine. The rising incidence and prevalence of hyperuricemia are probably related to the increased lifetime of the population, increasing levels of obesity, sedentary lifestyles, and alterations in dietary habits. (Loeb, 1972; Weaver, 2008). It has been shown that serum uric acid is positively associated with serum glucose levels in healthy controls (Clausen et al., 1998). It has been demonstrated that uric acid levels are higher in subjects with type–II DM than in healthy controls (Choukem et al., 2016). Furthermore, an elevated serum uric acid level was found to extend the possibilities and purpose of developing type –II diabetes in individuals with impaired glucose tolerance (Kodama et al., 2009). Hyperuricemia has also been added to the set of metabolic abnormalities associated with insulin resistance and/or increased the insulin secretion in metabolic syndrome (Niskanen et al., 2006). An elevated uric acid level as reported often precedes the event of obesity, hyperinsulinemia and diabetes (Conen et al., 2004).

Vitamin D plays an important role in whole-body calcium homeostasis by exerting significant influence on the duodenum, bone and kidney. Vitamin D can also alter intracellular calcium signals and plays an important role in pancreatic secretion and insulin sensitivity, and both of which are related to calcium levels. Vitamin D exerts a crucial role in the prevention of type II DM (Girgis et al., 2013, 2014).

Interestingly, vitamin-C being a potent antioxidant shares a structural similarity with glucose and therefore competes with glucose receptors in entering into the cells and affects insulin secretion, thus making it as a vital factor in diabetes. (Mann, 1974). Since, oxidative stress can cause disturbed glucose metabolism and hyperglycemia (Opara, 2004), supplementation of antioxidants could forestall diabetes or helps to attain positive outcomes in type-II Diabetes. Though diabetes is not traditionally considered a risk factor for antioxidant deficiency, patients with diabetes should all receive dietary advice about healthy eating and water-soluble vitamin dietary sources, including fresh fruits and vegetables. Numerous reports suggest that diabetic patients may have increased cellular uptake and turnover of antioxidants that may necessitate increased intake, and that may lead to even increased risk of deficiency (Will and Byers, 1996).

On the other hand, magnesium, being the second most abundant intracellular cation (Pham et al., 2007; Hans et al., 2002) is very important for over 300 biochemical reactions (Faryadi, 2012). In fact, magnesium is additionally required for insulin secretion (Rasic et al., 2004). The pancreatic cell cycle requires magnesium for its maintenance. Extracellular magnesium may regulate the ATP-sensitive potassium channels within the beta cells. This successively increases the intracellular calcium levels. The increased intracellular calcium levels are accountable for the discharge of insulin from the storage

granules (Ishizuka et al., 1994; Elamin and Tuvemo et al., 1990). Magnesium encompasses an explicit role in insulin hormone receptor interaction and favors the glucose entry into the cells (Rasic et al., 2004). In India, hypomagnesemia occurs in both type-I and II diabetes patients (Diwan et al., 2006). Apparently, hypomagnesaemia was observed to be a powerful independent predictor of type-II diabetes (Shaik et al., 2011; Anjum et al., 2012). Several studies have shown the association between hypomagnesemia and various complications of type-II DM like neuropathy, retinopathy and foot ulcers (Faryadi, 2012; Takaya et al., 2004), suggesting the correlation between serum magnesium and diabetes severity (Badyal et al., 2011). In hypomagnesemia conditions, defective tyrosine kinase activity was noticed at the insulin receptor levels, which causes impaired insulin interaction with the insulin receptor, leading to defective insulin resistance (Sharma et al., 2007). Conversely, osmotic diuresis and hypolipidemic agents, increase the urinary excretion of magnesium, which causes hypomagnesemia in diabetes, suggesting that hypomagnesemia can be a consequence of DM (Abou-Seif et al., 2004& Paolisso et al., 1988).

Essentially, alterations in calcium flux can have adverse effects on insulin secretion, a calcium-dependent process. An interesting study reported that calcium supplementation alone normalized glucose tolerance and insulin secretion in vitamin D depleted rats without diabetes (Huerta et al., 2005). Dysregulation of insulin receptor phosphorylation, a calcium-dependent process, alters insulin signal transduction and decreased glucose transporter activity. Moreover, changes in calcium levels modulate adiposity metabolism, which can promote triglyceride accumulation through increased de novo lipogenesis. Therefore, inability to suppress insulin-mediated lipolysis results in increased fat accumulation leading to obesity. It has been reported that patients with type-II DM exhibit impaired cellular calcium homeostasis including defects in skeletal muscle, adipocytes and liver (Huerta et al., 2005).

There are numerous reports on the status of these biochemical parameters associated with type-II DM, however, there are no studies available on these parameters in type-II DM patients of Kadapa area. Hence, the present study was designed to evaluate the status of key biochemical parameters associated with type-II DM in Kadapa urban area. These parameters would further help us to compare with the COVID-19 affected diabetic patients in our future study.

MATERIALS AND METHODS

Experimental subjects

The present study was conducted at Fathima Medical College, Kadapa. We recruited 100 type-II Diabetic patients and 100 healthy volunteers of age groups ranging between 40 and 70 years in the present study. Five ml of fasting blood samples and 3 ml of whole blood samples were collected in the clinical biochemistry laboratory for the estimation of fasting blood glucose (FBS) and 2 hour postprandial blood glucose (PPBG), by GOD-POD method. Serum uric acid, magnesium and calcium were estimated by IFCC approved clinical chemistry analyzer (fully automated). The lipid profile analyzed included total cholesterol, triglycerides, HDL, LDL and VLDL. The estimation of lipid profile was done by the CHOD-PAP and GPO methods. The VLDL was calculated by Friede-wald's and Fredrickson's formula (VLDL=TG/5). Serum vitamin C was estimated by 2,4-dinitrophenylhydrazine method and vitamin D was estimated by CMIA method.

Inclusion criteria:

- Patients with Type-II DM in the age group of 40-70 years in the Kadapa urban population.
- Genders: Both males and females are included.

Exclusion criteria:

- Type- I DM
- Pregnant women with gestational diabetes mellitus (GDM)

- Patients with hypertension
- Individuals with history of alcoholism
- Patients with cardiac and renal diseases

Statistical analysis:

Statistical analysis was carried out by using the SPSS software, version 20. Data were expressed as an arithmetic mean ± SD (standard deviation), a median, and maximum and minimum range with respect to their distribution.

Ethical approval:

The current study involving human participants were conducted after getting prior ethical approval (FIMSIEC/AP/08/2022). Informed consent was obtained from all individual participants included in the present study.

RESULTS AND DISCUSSION

The present study explores the status of biochemical parameters associated with Type-II DM in the cases of Kadapa population. Our study included a total of 200 subjects, of which 100 were Type-II DM patients and 100 were control (Normal subjects). Among 200 subjects participated in the study, 116 were males and 84 were females. The group comprising of diabetes cases had 100 subjects, of which 60 were males and 40 were females. The group comprising of controls had 100 subjects, among which 56 were males and 44 were females. There was no statistically significant difference between cases and controls with respect to age and sex (Table 1).

Table 2 shows that the levels of serum FBS, PPBS and uric acid in Type-II Diabetic cases and controls, wherein the levels were increased significantly when compared to healthy control subjects in Kadapa area. Chronic high glucose concentration was reported to cause muscle loss, which in turn leads to increased non-protein nitrogen substances such as uric acid. Hyperuricemia is associated with obesity and insulin resistance, and consequently with type-II diabetes (Yoo et al., 2005; Baker et al., 2005).

The serum levels of total cholesterol, TGL and LDL in Type-II diabetic cases were increased significantly when compared to healthy control subjects in Kadapa area (Table 3). However, the serum levels of HDL in Type-II diabetic cases were decreased significantly when compared to healthy control subjects. The study shows a positive correlation between serum uric acid and total cholesterol, TGL, and LDL and a significant negative correlation between serum uric acid and HDL. Further, increased uric acid levels were observed in Type-II diabetic patients, which indicate a positive relationship between uric acid and cholesterol in Type-II diabetic cases (Prashanth Kumar et al., 2015).

The levels of serum magnesium and calcium in Type-II Diabetic cases were also found to be decreased when compared to healthy control subjects in Kadapa area (Table 4). Magnesium is involved in various chemical reactions associated with the regulation of insulin signaling such as phosphorylation of insulin receptor kinase, post-receptor action of insulin, and insulin-mediated cellular glucose uptake (Barbagallo & Dominguez, 2007)**.** Several studies have shown the association between hypomagnesemia and various complications of Type-II DM like neuropathy, retinopathy, foot ulcers, etc. (Faryadi, 2012; Takaya et al., 2004; Badyal et al., 2011). In hypomagnesemia conditions, defective tyrosine kinase activity was noticed at the insulin receptor levels, which causes impaired insulin interaction with the insulin receptor, leading to defective insulin resistance (Sharma et al., 2007). Conversely, osmotic diuresis, hypolipidemic agents, etc. increases urinary excretion of magnesium, leading to the onset of hypomagnesemia in diabetes (Abou-Seif et al., 2004; Paolisso et al., 1988).

Essentially, alterations in calcium flux can have adverse effects on insulin secretion, a calcium-dependent process. An interesting study reported that calcium supplementation alone normalized glucose tolerance and insulin secretion in vitamin D-depleted rats without diabetes (Huerta et al., 2005). Dysregulation of insulin receptor phosphorylation, a calcium-dependent process, alters insulin signal transduction and decreased glucose transporter activity. Table 4 displays the serum levels of vitamin D

and vitamin C in Type-II diabetic cases when compared to healthy control subjects in Kadapa area. A significant decrease in the serum vitamin D and C levels was observed between the diabetic cases and control samples. Further, Chen et al. (2005) reported that since both glucose and vitamin C competes for glucose transporters due to their structural similarities, vitamin C gets excluded from the cells under hyperglycemic condition. Exclusion of vitamin C leads to the accumulation of reactive oxygen species (ROS) due to the reduction in the antioxidant capacity of the cells. Interestingly, no scientific evidence exists in Kadapa area about the status and importance of vitamin D and C levels in Type-II diabetic cases. Further, since vitamin C shares a structural similarity with glucose, it affects the insulin secretion, thus enhancing the severity of DM and increasing oxidative stress during diabetic condition. Hence, the present study would create awareness to the Type-II DM patients in Kadapa area to concentrate on the levels of vitamins C and D and diet patterns, accordingly.

CONCLUSION

In conclusion, our present study documents that Type-II DM patients in Kadapa area were associated with hypercholesterolemia and lowered vitamin C and D levels. Hence, our study highlights the importance of vitamins in diabetes.

CONFLICT OF INTEREST: None.

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Table Legends

Table 1. Status of sociodemographic variables between control and Type-II DM cases. The "*p*" value is not statistically significant between cases (Type-II DM) and control (Normal Subjects) with respect to age and sex (*0.3475*).

Table 2. Shows the levels of FBS, PPBS and uric acid in healthy control subjects and patients with Type-II DM. The mean values of FBS, PPBS and uric acid were higher in cases than in controls. The "*p*" value is statistically significant for FBS, PPBS and uric acid (< 0.0001).

Table 3. Status of lipid profile in healthy control subjects and patients with Type-II DM. The mean values of total cholesterol, triglycerides and LDL were higher in cases than in controls. The mean value of HDL was lower in cases than in controls. The "*p*" value is statistically significant for total cholesterol, triglycerides, LDL and HDL (< 0.0001).

Table 4. Levels of magnesium, calcium, vitamin D and vitamin C in control and Type-II DM cases. The mean values of magnesium, calcium and vitamin D were lower in cases than in controls. The "*p*" value is statistically significant for magnesium, calcium and vitamin D (<0.0001). The mean value of vitamin C was lower in cases than in controls. The "*p*" value is statistically significant for vitamin C (0.0015).

Table 1.

Sociodemographic Variables	**Control**	**Cases**	**'p value'**
Age (Years)	55.00±8.86	56.24±9.74	0.3475
Sex (Male/Female)	Males–56 Females–44	Males–60 Females–40	

Table 2.

Parameters	**Control**	**Cases**	**'p value'**
FBS (mg/dL)	77.26±9.29	195.97±15.73	<0.0001
PPBS (mg/dL)	113.56±12.29	261.27±49.58	<0.0001
Uric acid (mg/dL)	4.508±0.816	6.828±1.059	<0.0001

Table 3.

Parameters	**Control**	**Cases**	**'p value'**
Total cholesterol (mg/dL)	138.06±18.57	246.91±55.07	<0.0001
Triglyceride (mg/dL)	97.24±18.81	150.85±37.28	<0.0001
HDL (mg/dL)	41.48±3.32	33.94±7.28	<0.0001
LDL (mg/dL)	77.168±16.99	182.756±54.679	<0.0001

Table 4.

Parameters	**Control**	**Cases**	**'p value'**
Magnesium (mg/dL)	2.336±0.299	1.480±0.448	<0.0001
Calcium (mg/dL)	9.590±0.451	8.305±0.858	<0.0001
Vitamin D (ng/mL)	35.865±5.847	24.145±6.451	<0.0001
Vitamin C (mg/dL)	1.262±0.172	1.052±0.628	0.0015