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A Study to Assess and Correlate Serum Levels of Creatinine with Muscle Mass among Patients with Diabetes and Prediabetes at a Tertiary Care Hospital in Uttarakhand

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ABSTRACT

Background: Low skeletal muscle mass is coupled with insulin resistance and metabolic syndrome. 24 hours urinary creatinine excretion is positively correlated with muscle mass. Hence, we have conducted this study to find if serum levels can be correlated to muscle mass and if there is a possibility of difference in levels in those who have diabetes and prediabetes.

Materials and Methods: In this clinic-based cross-sectional study involving 140 subjects, either sex were recruited. They were divided into three groups (Group 1: Diabetic, Group 2: Pre-diabetics, Group 3: Healthy controls). Their detailed histories and anthropometric measurements were taken, and the blood sample was collected to estimate plasma glucose and serum creatinine.

Settings and Design: It was a clinic-based cross-sectional study. Patients attending OPD of AIIMS, Rishikesh with prediabetes and diabetes were included in the study. Healthy controls were randomly selected from the people working in AIIMS, Rishikesh.

Results: On comparison with controls, serum creatinine levels were significantly lower [P <0.05] in pre-diabetics with a further significant reduction in the case of diabetics [P <0.05]. Although the values were lower in diabetics than controls, the muscle mass had no significant difference between the three groups. The serum creatinine levels revealed a direct correlation with muscle mass in Group 3 (non-diabetic controls) as well as Group 1 (diabetic males and females). However, the correlation of serum creatinine levels with muscle mass was not found to be statistically significant in Group 2 (pre-diabetics).

Conclusion: Serum creatinine levels can be used as a marker for measurement of muscle mass in the patients suffering from diabetes mellitus since low muscle mass is a risk for insulin resistance and metabolic syndrome.

KEYWORDS: *Muscle mass; Creatinine; eGFR; Calculated arm muscle area (CAMA); Insulin resistance; Metabolic syndrome*

INTRODUCTION

India is the diabetes capital of the world [1]. There is a tremendous surge in diabetes mellitus in Uttarakhand regions, with 5.7% prevalence [2]. It has been shown in many studies that low skeletal muscle mass is coupled with insulin resistance and

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metabolic syndrome [3]. The simple anthropometric measurement of the mid-arm circumference (cm) and triceps skin fold measurement (mm) can be used for muscle mass calculations [4]. The same formula has been used in India settings also [5]. Creatine is a high energy compound located mainly in striated muscle (98%). Its spontaneous dehydration results in the formation of creatinine, which is an excretory product. 24 hours urinary creatinine excretion is highly correlated with muscle mass [6]. But serum creatinine is also positively associated with creatinine 24 hours urinary excretion in normal renal function subjects. Hence it may be considered as a satisfactory and easily measured surrogate marker of muscle mass. In this study, we attempted to find if serum levels can be correlated to muscle mass and if there is a possibility of difference in levels in those who are diabetes and prediabetes. A probable relationship between low serum creatinine and diabetes has of late invoked a lot of interest and has been demonstrated [7,8]. In the present study, we aim to corroborate this finding in our settings.

SUBJECTS AND METHODS

It was a clinic-based cross-sectional study. Patients attending OPD of AIIMS, Rishikesh with prediabetes, and diabetes were included in the study. Healthy controls were randomly selected from the people working in AIIMS, Rishikesh.

Study participants were recruited as per the following inclusion/exclusion criteria.

Inclusion Criteria

1. The diagnosis of T2DM was based on the World Health Organization criteria [9].
   Fasting >126 mg/dl or 2 hours Post prandial >200 mg/dl or both.
2. Criteria for prediabetes were adapted from The International Expert Committee [10].
   IFG (impaired fasting glycemia)
   - FPG: 100 mg/dL to 125 mg/dL

   IGT (impaired glucose tolerance)
   - FPG less than 100 mg/dL

   2 hours Post prandial: 140 mg/dL to 199 mg/dL
3. Those having estimated glomerular filtration rate (eGFR) more than 60 ml/min/1.73 m^2

Exclusion Criteria

Potential study subjects were excluded if:

1. Patients presented with symptoms suggestive of type 1 diabetes, defined as diabetic ketoacidosis, an acute presentation with heavy ketonuria, or continuous insulin requirement within 1 year of diagnosis.
2. Patients with a diagnosis of urinary tract infection, urolithiasis, liver cirrhosis, congestive heart failure, macro vascular diseases, overt proteinuria, or other known major diseases were also excluded based on interview physical examination, and urinalysis.
3. Concurrence of any systemic disease.
4. Pregnancy.
5. Drugs influencing body weight like corticoids or contraceptives.

Sample Size

Ninety patients of Patients attending OPD of AIIMS, Rishikesh with prediabetes, and diabetes were included in the study, and healthy controls were randomly selected from the people working in AIIMS, Rishikesh.

From those found suitable for enrolment in the study, informed consent was taken. Ethical clearance was obtained from the Institute Ethical Committee before the research was conducted (Reference Number: AIIMS/IEC/16/12).

Anthropometric Measurements

Anthropometric and skin fold measurements were carried out on the subject after recruitment. Subjects were weighed in minimal clothing, using a digital balance. The subjects' height was recorded, without footwear, using a stadiometer and expressed to the nearest 0.1 cm.

Anthropometric parameters measured included calculated parameters like body mass index (BMI) and waist to hip ratio (WHR).

Body mass index (BMI) was calculated from the height and weight as follows; BMI = weight (kg)/height 2 (m).

Waist and hip circumferences were measured to the nearest 0.1 cm at the narrowest point between the lowest rib and the uppermost lateral border of the right iliac crest. The hips were measured at their widest point.

The mid-arm circumference (MAC) was measured with the subject standing erect and elbow flexed to 90º with the midpoint between the tip of the acromion and the olecranon process being located. The tape was placed at the midpoint, and measurement was done with the arm relaxed, elbow extended to the nearest 0.1 cm.

Triceps skin fold measurement was taken in the standing position, and the mean was taken for further calculation. The triceps skin fold was measured in the midline of the posterior aspect of the arm, over the triceps muscle, at a point midway between the lateral projection of the scapula's acromion process and the inferior margin of the olecranon process of the ulna.

The skin fold measurement was carried out to the nearest 0.2 mm using skin fold caliper.

The physical activity was also assessed using a questionnaire. The Hindi version was made following the forward-backward translation procedure. The physical activity questionnaire was shown to five experts, and it was modified according to their suggestions. Pilot testing of the modified questionnaire was done using responses from 20 students.

A trained nurse took seated blood pressure after the subjects had rested for 5 minutes.

Two ml overnight fasting blood sample was collected by phlebotomist after informed consent. The blood samples were analyzed for serum creatinine using Jaffe's kinetic method and plasma glucose using the glucose oxidase peroxidase method.

Besides, the following calculations were used:

1. **Estimated glomerular filtration rate (eGFR):** Calculated using the Cockcroft Gault formula [11].

eGFR= (140 - age)(weight in kg) × k*/72 × serum creatinine (mg/100mL)

*k is 1 in males and 0.85 in females

2. **Calculation of muscle mass:** The mid-arm circumference (MAC in cm) and triceps skin fold measured (TSF in mm) to calculate corrected arm muscle area (CAMA).

CAMA in males = (MAC - pi x TSF) $^{2}/^{4}$ pi] - 10

CAMA in females = (MAC - pi x TSF) $^{2}/^{4}$ pi]-6.5

Total body muscle mass (kg) was calculated from CAMA using a prediction equation that related CAMA and height to weight.

Muscle mass (kg) = [(0.309 × Weight) + (0.202 × CAMA) + 4.971]

Results of the following tests were intimated to participants.

Statistical analysis was done to assess the statistically significant association of independent variable with dependent variable through Chi^2 test, correlation and logistic regression etc.

RESULTS

The study comprises 140 subjects, 90 randomly selected from the outpatients department of Medicine, AIIMS, Rishikesh with diagnosed prediabetes, and diabetes. Based on the previous history for old patients (follow up cases of diabetes or prediabetes) or based on plasma glucose values as per inclusion criteria, the patents were included in the study. Healthy controls were randomly selected from the people working in AIIMS, Rishikesh. They have undergone routine medical check-up and then were enrolled as the control group. After intimating the study's objectives and taking written informed consent, study subjects were enrolled in a question/answer session. Study subjects were assisted in completing a structured questionnaire that contained information about physical activity. Ethical clearance was obtained from the Institute Ethical Committee before the research was conducted (Reference Number: AIIMS/IEC/16/12).

Their detailed histories and anthropometric measurements were taken, and a blood sample was collected to estimate blood glucose and serum creatinine. 140 study subjects were divided into the following groups:

Group 1: Comprised of 50 cases suffering from diabetes mellitus.
Group 2: Comprised of 40 cases suffering from prediabetes.
Group 3: Comprised of 50 healthy controls.

The mean ages of Group 1 (diabetic) and Group 2 (pre-diabetics) were 52.52 + 12.63 and 50.38 + 11.22 years, respectively. The sex ratio (male to female) of the study was 1.66 and 1.5, respectively. Healthy individuals were selected from AIIMS, Rishikesh staff as controls.

Out of the 50 controls, 14% were unemployed, and 78% were involved in sedentary activities like office and clerical work, whereas 8% performed moderate activities. None of the controls were involved in strenuous work. The percentage of unemployed in the pre-diabetic group was 35%. In this group, most people (60%) indulged in sedentary activity; only 5% in

Group 2 had moderate activity. Among Group 1 (people with diabetes), 38% of people were either retired or were currently unemployed, whereas the significant chunk of 50% was sedentary. Only 8% were performing strenuous activities.

In comparison with controls, serum creatinine levels were significantly lower [P <0.05] in pre-diabetics with a further significant reduction in the case of Diabetics [P <0.05]. The mean values of serum creatinine are depicted in Table 1. Although the values were lower in Diabetics than controls, the muscle mass had no significant difference between the three groups. The serum creatinine levels revealed a direct correlation with muscle mass in Group 3 (Non-Diabetic controls) as well as Group 1 (diabetic males and females). Although the correlation of serum creatinine levels with muscle mass was not found to be statistically significant in Group 2 (pre-diabetics), as shown in Table 2.

	Group 1 {Diabetes(n=50)}	Group 2 {Prediabetes(n=40)}	Group 3 {Control(n=50)}
Serum Creatinine [Mean±SD]mg/dl	0.78±0.16	0.82±0.18	1.10±0.13
Muscle Mass [Mean±SD]kg	24.67±4.01	24.79±3.92	25.49±3.51

Table 1: Serum creatinine levels and muscle mass in different groups.

	Group1 {Diabetes(n=50)}	Group2 {Diabetes(n=50)}	Group3 {Diabetes(n=50)}
Serum Creatinine [Mean±SD] mg/dl	0.78±0.16	0.82±0.18	1.10±0.13
Muscle Mass [Mean±SD]kg	24.67±4.01	24.79±3.92	25.49±3.51
Pearson correlation (p value)	.025 (significant)	.780 (insignificant)	.007 (significant)

Table 2: Correlation of serum creatinine levels with muscle mass in pre-diabetics, diabetics and non-diabetics.

DISCUSSION

The present study has given us male to female ratio to be 1.66 and 1.5, respectively, in Group 1 and 2. This is reflected in many previous studies indicating that the prevalence of diabetes is higher among men than women worldwide [12,13]. This gender bias has to be further studied as research has highlighted that men and women differ in their care-male diagnosis leads towards much more changes in family eating habits than females. The gender difference also exists regarding understanding after attending a structured diabetes education program [14].

In the present study on comparison with controls, the serum creatinine levels were significantly lower [P <0.05] in pre-diabetics with further reduction in the case of diabetics [P <0.05]. Many studies previously have described the association of low serum creatinine with the risk of developing type 2 diabetes mellitus. Nobuko Harita et al. did a large prospective study, including 877 men with a follow-up period of 4 years. They found that lower serum creatinine was associated with an escalated risk of type 2 diabetes [15]. They suggested a declining trend of the serum creatinine levels with increasing blood glucose levels. In another study, Jøran Hjelmeaeth et al. concluded that low serum creatinine is a predictor of type 2 diabetes in cucasian morbidly obese patients, this being independent of established risk factors like a family history of diabetes, or deranged anthropometry, age, gender, concomitant hypertension, and smoking [16].

A decrease in the creatinine levels in prediabetes has not been prospectively studied. However, a study by Srikanthan et al. correlated the muscle mass with insulin resistance and found an inverse association between relative muscle mass and insulin resistance in pre-diabetics [17]. In our study, the muscle mass values were lower in diabetics than controls, but this difference was not statistically significant.

Our study results show a significant statistical correlation in the serum creatinine levels with muscle mass in diabetics and non-diabetics. This may reflect that diabetes tends to enhance muscle loss with increasing age and protein anabolism is abnormal in diabetics [18]. However, the correlation was not statistically significant in pre-diabetics. Serum creatinine has been previously studied as a surrogate marker of muscle mass [19] with new emerging data reviving the notion that serum creatinine levels are a reliable marker of muscle mass, but this is confined to studies on chronic dialysis patients. Literature is also available on the measuring of creatinine turnover using 24 hours urine collection as a surrogate marker.

Our results may reflect the fact that a lower volume of skeletal muscle would mean fewer target sites for insulin, and this may explain lower serum creatinine in diabetics and pre-diabetics. Diabetes-related triggering of mechanisms shows negative regulation of skeletal muscle mass. One study has pointed at the increased expression of myostatin mRNA in people with diabetes. Myostatin is a peptide hormone known to impact muscle mass [20] negatively.

Obesity seems to be related to this. Studies have shown that the 52 kDa myostatin precursor protein expression is significantly elevated in cells cultured from extremely obese compared with cells obtained from lean non-obese donors [21]. Aging also is known to play a role in preventing the anabolic effect of insulin on muscles. Physiological hyperinsulinemia stimulates muscle protein synthesis and anabolism in young subjects; however, aging is associated with an inability of insulin to stimulate muscle protein synthesis and net amino acid uptake even in healthy, glucose tolerant persons [22]. This defect has been associated with a blunted mammalian target of rapamycin (mTOR) signaling and endothelial dysfunction, limiting muscle perfusion and protein anabolism in older adults [23].

Thus the loss of muscle mass in diabetics may be involving multiple pathways, enhancing negative signals like myostatin and down regulation of positive anabolic signaling of insulin. Muscle protein anabolism in diabetes is resistant to insulin action but perhaps not to exercise or amino acid supply. Amino acid supplementation and exercise programs may improve muscle mass and function in persons with diabetes, preventing long term morbidities.

CONCLUSION

In this study, we attempted to find if serum levels can be correlated to muscle mass and if there is a possibility of difference in levels in those who are diabetes and prediabetes. The results point at the correlation between muscle mass and serum creatinine levels among diabetics and non-diabetics to be significantly correlated, whereas it was not so for pre-diabetics. Compared with controls, serum creatinine levels were significantly lower in Pre-diabetics and Diabetics [$P < 0.05$]. The muscle mass values were lower in diabetics than controls, but there was not a statistically significant difference between the three groups. Our study's limitation was the small sample size and its cross-sectional design, so further studies addressing the multiple pathways involved with a larger sample size may provide more information.

The present study was designed to look for the correlation of serum creatinine levels with muscle mass in patients of diabetes mellitus and prediabetes. The study aimed to know the trend of serum creatinine levels in the sufferers of diabetes mellitus since low muscle mass is a risk for insulin resistance and metabolic syndrome.

In the present study, the correlation between muscle mass and serum creatinine levels among diabetics and non-diabetics were significantly correlated, whereas it was not so for pre-diabetics. In comparison with controls, serum creatinine levels

were significantly lower in pre-diabetics and diabetics. The muscle mass values were lower in diabetics than controls, but there was no statistically significant difference between the three groups. The present study has tried to fill the knowledge gap being a pilot study in hospital settings. It has provided a backdrop for a broader community-based study addressing the multiple pathways involved and the interventions that may help prevent muscle loss in diabetics.

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