



## **Role of Microalbuminuria and Insulin Resistance as Predictive Biomarkers for Nephropathy in Obese Individuals – A Study Protocol**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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**Study Protocol**

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### **ABSTRACT**

**Background:** Obesity is a compounded, multifactorial, and largely curable disease, affecting over a third of the public community today. The World Health Organization (WHO) has declared obesity as a global epidemic, also stressing that in many cases it remains an under-recognized problem of the public health agenda. It is a global health concern and a major risk factor for diabetes, hypertension, and dyslipidemia, which may lead to decrease in renal function and ultimately obesity related nephropathy.

As per, the epidemiological and experimental data have indicated, microalbuminuria (MAU) is an early marker of target organ damage and is associated with all-cause mortality, cardiovascular diseases (CVDs) incidence, and progression of nephropathy in non-diabetic subjects. Insulin resistance is present in obese individuals. Obesity related insulin resistance may arise from defects in fatty acid oxidation, and secondary  $\beta$ -cell lipotoxicity.

The present study is a Cross-sectional analytical observational study; the study will be carried out in the Dept. of Biochemistry at Jawaharlal Nehru Medical College, ABV Rural Hospital, Sawangi (M), Wardha. Participants will be outpatients of this institution. Any participant fulfilling the eligibility criteria will be included in the study. Protocol amendments are not expected. However, if necessary, any modification to the protocol will be reported to the entire investigational team through a conference. All changes will be included in the final manuscript prior to submission.

**Aim and Objectives:** Present study is targeted to assess role and correlation of microalbuminuria and insulin resistance as predictive biomarkers for nephropathy in obese subjects.

**Implications:** Present study will be helpful to decrease morbidity and mortality, specifically associated with compromised renal status and prevent nephropathy. The study will be helpful to detect early clinicopathological phase of compromised renal status.

**Conclusion:** The purpose of this study is to investigate role of microalbuminuria and insulin resistance as predictive markers of nephropathy in obese individuals.

*Keywords: Obesity; microalbuminuria; insulin resistance; kidney disease; nephropathy.*

## 1. INTRODUCTION

Obesity is a complex, multifactorial disease, with genetic, behavioral, socioeconomic, and environmental origins, obesity raises the risk of debilitating morbidity and mortality. [1] with a predicted rise in the global obesity prevalence to 18% in men and surpass 21% in women by 2025. [2] The more conservative projection, which only considered changes in population and urbanization but not secular trends in prevalence, indicates that the numbers of overweight and obese individuals will increase by 44 and 45%, respectively, from 2005 estimates, totaling to 1.35 billion overweight and 573 million obese individuals in 2030. If recent secular trends continue unabated, the absolute numbers could rise to a total of 2.16 billion overweight and 1.12 billion obese.[3] The World Health Organization (WHO) has declared obesity as a global epidemic, also stressing that in many cases it remains an under-recognized problem of the public health agenda.[3, 4]

Obesity greatly increases risk of chronic diseases namely type 2 diabetes, cardiovascular disease and associated mortality.[1]South Asian population from India, Nepal, Bangladesh, Bhutan, Maldives, Sri Lanka and Pakistan are 3 times more prone to develop obesity and its associated complications. [5] It is a global health concern and a major risk factor for diabetes, hypertension, and dyslipidemia, which may lead to decrease in renal function and ultimately obesity related nephropathy.[6]

Microalbuminuria is known as an early clinical manifestation of diabetic nephropathy. Microalbuminuria (MAU) is a common subclinical

disease whose prevalence ranges from 5–7% in the general population[7] Micro albuminuria, defined as 30–300 mg albumin/day or 30–300 mg albumin/g creatinine (Cr) excreted in the urine, often degenerates to normoalbuminuria (< 30 mg/gCr). In contrast, regression may be associated with non-glomerular complications as, in some diabetic patients with chronic kidney disease normoalbuminuria is seen without any retinopathy.[8,9]Microalbuminuria (MAU) is an established predictor of micro and macro vascular complications in patients with type 2 diabetes. Recent studies showed that micro albuminuria is a predictor of cardiovascular disease and nephropathy in subjects without diabetes[9]

As per, the epidemiological and experimental data have indicated that MAU is an early marker of target organ damage and is associated with all-cause mortality, Cardio vascular diseases incidence, and progression of nephropathy in non-diabetic subjects. [9, 10]

Approximately 30-40% of patients with type 2 diabetes develop microalbuminuria [10], which in 5–10% of case subjects may already be present at the diagnosis of the disease [11, 12]. Every year, 2–5% of those with normal urinary albumin excretion develop microalbuminuria [12, 13], 2–3% of those with microalbuminuria progress to macroalbuminuria [12, 14] and 2–3% of those with macroalbuminuria progress to renal insufficiency that may ultimately require dialysis or transplantation. [15]In addition, several studies have reported that insulin resistance or pre-diabetes is associated with MAU. However, few studies have explored the effect of MAU on the development of diabetes in the non-diabetic population and there is a link between obesity

and kidney injury leading to chronic kidney disease and it is of major concern in pediatric population. Overall microalbuminuria and serum cystatin C can be used as reliable biomarkers in child hood obesity.[16, 17] A reduction in central obesity should be emphasized as a key component for the prevention of vascular and renal function decline. [18, 19]

The term 'insulin resistance' refers to a decrease in a target cell's metabolic response to insulin, or, at the whole-organism level, an impaired lowering effect of circulating or injected insulin on blood glucose. [20]Insulin resistant status normally precedes the onset of diabetes by 1 to 2 decades. It is largely sustained by acquired factors such as decreased physical activity and obesity. [21]Insulin resistance is present in obese individuals. Obesity related insulin resistance may arise from defects in fatty acid oxidation [22], and secondary  $\beta$ -cell lipotoxicity [23]

Evidence suggests that insulin resistance precedes and contributes to the development of microalbuminuria in type 1 diabetic patients [21] and in non-diabetic subjects [24]

Hence individuals with obesity are more prone to develop insulin resistance and microalbuminuria. Both the parameters microalbuminuria and insulin resistance can be used as predictive markers of obesity associated nephropathy as these markers seem to be altered most early in obese individuals.

The purpose of this study is to investigate role of microalbuminuria and insulin resistance as predictive markers of nephropathy in obese individuals. It is focused to assess the role of microalbuminuria and insulin resistance as predictive markers and important flag signs for assessment for nephropathy in obese individuals. Central obesity is also associated with the metabolic syndrome and insulin resistance (IR) along with the progression of renal disease. Several anthropometric studies have reported that microalbuminuria is related to central obesity.[25,26, 27]

## 1.1 Hypotheses

### 1.1.1 Null hypothesis

There is no statistically significant role of MAU & IR as predictive biomarkers in development of progressive nephropathy in obese individuals.

### 1.1.2 Alternative hypothesis

There is statistically significant role of MAU & IR as predictive biomarkers in development of nephropathy in obese individuals.

### 1.1.3 Research gap

There are numerous studies conducted to evaluate role of microalbuminuria and insulin resistance with diabetes mellitus, hypertension, however the assessing microalbuminuria and Insulin resistance as biomarkers for predicting nephropathy in obese individuals needs to be further established, further these markers can be utilized to devise a predicting scale for aiding in compromised renal status.

## 1.2 Research Question

Can microalbuminuria and insulin resistance be established as predictive biomarkers to prevent nephropathy in obese individuals?

## 2. MATERIALS AND METHODS

The present study is a Cross-sectional analytical observational study; the study will be carried out in the Dept. of Biochemistry at Jawaharlal Nehru Medical College, ABV Rural Hospital, Sawangi (M), Wardha. Participants will be outpatients of this institution. Any participant fulfilling the eligibility criteria will be included in the study. Protocol amendments are not expected. However, if necessary, any modification to the protocol will be reported to the entire investigational team through a conference. All changes will be included in the final manuscript prior to journal submission.

### 2.1 Aim and Objectives

#### 2.1.1 Aim

To assess role of microalbuminuria and insulin resistance as predictor biomarker for *progressive* nephropathy in obese subjects.

#### 2.1.2 Objectives

- To categorize individuals as obese and further establish their metabolic healthy/unhealthy status
- To estimate microalbuminuria in obese subjects
- To estimate insulin resistance in obese subjects

- To evaluate the renal status in obese subjects
- To assess the correlation of microalbuminuria and insulin resistance as predictive biomarkers for nephropathy in obese subjects.

## 2.2 Sample Size

Sample size for study is calculated on the basis of inclusion criteria to find out the correlation. Where  $\alpha = 5\% = 0.05$  (error / level of significance)  $\beta = 20\% = 0.2 = [1 - \beta] = 0.8$  (type 2 error)  $r = 20\% = 0.2$  (expected correlation/ correlation coefficient)

$$C = \frac{1}{2} \ln \left[ \frac{(1+r)}{(1-r)} \right] \text{ (natural logarithm)}$$

$$N = \left[ \frac{(Z\alpha + Z\beta)^2}{C^2} \right] + 3 = 194$$

Sample size for the study will be 194-200

### 2.2.1 Study participants

Obese subject attending medicine OPD at AVB Rural Hospital, Sawangi, Meghe will be included in the study. Classifications of age group will be done as 0–14 years old (paediatric group), 15–47 years old (youth group), 48–63 years old (middle-aged group), and  $\geq 64$  years old (elderly group).

### 2.2.2 Inclusion criteria

For the participants will be as follows: Consciously well obese subjects, BMI 30 kg/m<sup>2</sup> or over, willing to participate will be included.

### 2.2.3 Exclusion criteria

The patient of mental disorder, thyroid disorder, endocrine disease such as hypothyroidism, Cushing's syndrome, etc., conditions that could affect patient weight, other serious disorders and unwilling patients will be excluded from the study.

### 2.2.4 Criteria to define obesity

Body mass index (BMI) and Waist-to-hip ratio (WHR) will be assessed during a medical examination. BMI will be calculated as weight (in kilogram)/height (in meters) squared and WHR by dividing waist circumference by hip circumference. Abdominal obesity is further defined as waist–hip ratio above 0.90 for males and above 0.85 for females, or a BMI above 30.0 recommendation from WHO. According to the WHO, BMI will be categorized to normal weight (18.5–24.9) overweight (25.0–29.9), obesity I (30.0–34.9) & obesity II (35.0–39.9). [28]

General history of the participant will be taken as per the attached proforma along with the physical examination, systemic examination.

**Table 1. Following parameter will be analyzed**

S. No.	Parameters	Method
1.	Fasting Blood Sugar	( GOD-POD, Vitrous 5600) [29]
2.	Cholesterol	(CHOD-PAP)[30]
3.	Triglycerides	Triglycerides TG by glycerol phosphate oxidase. (GPO)-tinder method [31, 32,33]
4.	High Density Lipoprotein	Precipitationmethod[34]
5.	Low Density Lipoprotein and Very low density lipoprotein	Will be calculated by Friedewalds equation. [35]
6.	Microalbuminuria	Screening for microalbuminuria will be done by measurement of the albumin-to-creatinine ratio in morning urine or random sample or measurement of urine albumin in morning urine [36]
7.	Fasting Insulin	Insulin assays, CLIA, Vitrous 5600, USA machine with assay reagents and calibrators from Vitrous 5600, Dry Chemistry[37]
8.	HOMA IR	Score will be calculated as Glucose (mg/dl)×Insulin× 22.5, and a HOMA-IR score $\geq 2.5$ was taken as an indicator of IR [38-41]
9.	Serum Creatinine	Jaffe's method for estimation of creatinine[42]
10.	Estimated Glomerular Filtration Rate	Levey AS method for e GFR[43]

### 2.2.5 Collection and processing of blood sample

After overnight fasting five ml of venous blood will be collected from all the participants after, written and informed consent, in dry disposable syringe under aseptic precautions and will be transferred to a sterile, dry and acid washed vial for biochemical analysis.

## 3. EXPECTED RESULTS AND DISCUSSION

### 3.1 Statistical analysis

All estimated results will be expressed as mean  $\pm$ SD. Mean values will be assessed for significance by unpaired student  $-t$  test. Multiple regression analysis (MRA) will be done to predict the value of variable based on two or more other variable. Chi Square test will be done to examine the differences between categorical variables in the same population. A statistical analysis will be performed using the Statistical Package for the Social Science program (SPSS, 24.0). Frequencies and percentages will be used for the categorical measures. Probability values  $p < 0.05$  will be considered statistically significant.

## 4. CONCLUSION

MAU & IR shows significant derangement in obesity, specifically as a predictor for nephropathy. However, further research is essential to evaluate the role of microalbuminuria and insulin resistance especially obese individuals to prevent more serious diseases by screening obese patients for microalbuminuria and Insulin resistance.

### 4.1 Future Scope & Implications (probable)

Obesity has become substantial problem among different spectrum of women and men. The onset of obesity-associated renal disease is insidious and asymptomatic, so early markers will be extremely useful in its prevention and treatment. Present study will be helpful to decrease morbidity and mortality, specifically associated with comprised renal status and prevent nephropathy. The study will be helpful to detect early clinicopathological phase of comprised renal status.

## CONSENT AND ETHICAL APPROVAL

This study is conducted to comply, that the proposed research work will be carried out in accordance with the ethical guidelines prescribed by Central Ethics Committee on Human Research (C.E.C.H.R.). Present study has received the approval of the Institutional Ethics Committee, committee has approved the research work proposed to be carried out at Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Sawangi (Meghe), Wardha: Ref.No. DMIMS (DU)/IEC/2020-21/179.

Written informed consent will be obtained prior to the study by the investigator. The confidentiality of personal information will be ensured. Each participant will be assigned an identification number at enrolment. All records will remain secure in a locked cabinet or password-protected computer files, both for the duration of the study and after the study has concluded.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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