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Original Article

Biochemistry Section

Correlation of HbA1c and Insulin Resistance with Urine Albumin Excretion in Non Diabetic Obese Population: A Cross-sectional Study

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ABSTRACT

Introduction: A number of metabolic disorders are linked to obesity, which is a global health concern. Although renal impairment is a serious side-effect of obesity, its connection to insulin resistance is still a subject of discussion.

Aim: To assess the correlation between microalbuminuria and HbA1c levels, as well as the association between Insulin Resistance (IR) and renal function in obese individuals.

Materials and Methods: The present study was a cross-sectional study conducted in patients attending the obesity clinic, in Endocrinology department, of a tertiary hospital in Kerala, India. A total of 144 obese individuals participated, meeting age, Body Mass Index (BMI), and health-related. Insulin resistance was measured using Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), while renal function was measured using the Urine Albumin Creatinine Ratio (UACR). Correlation analysis was conducted to investigate relationships between variables.

Results: The study found a weak association between UACR and HbA1c levels and insulin resistance (r-value=0.159, p-value=0.056). Subjects with insulin resistance had significantly higher levels of microalbuminuria. Despite these connections, the mean UACR levels remained within the typical reference range.

Conclusion: This study emphasises the importance of early renal health screening in obese individuals, with HbA1c and microalbuminuria measurements as promising methods for preventing kidney impairment. To establish causation in the complex interplay between metabolic variables and renal function in obesity and insulin resistance, future research should focus on understanding the underlying mechanisms and conducting longitudinal examinations.

Keywords: Microalbuminuria, Renal function, Urine albumin creatinine ratio

INTRODUCTION

The global health epidemic of obesity has far-reaching effects on both the general public's health and individuals' personal well-being. The onset of IR, characterised by cells that are less responsive to insulin and resulting in higher blood sugar levels, is a particularly concerning side-effect of obesity. IR plays a crucial role in the development of type 2 diabetes mellitus and is associated with various metabolic abnormalities. Recent studies have examined the complex interaction between obesity, IR, and renal impairment, shedding light on the underlying mechanisms and emphasising the urgent need to understand this intricate interplay [1,2].

The relationship between obesity and IR involves intricate interactions between adipose tissue, inflammation, and metabolic processes, which have multiple facets [3]. The accumulation of excess fat, particularly in visceral adipose tissue, is a hallmark of obesity and can lead to cell-autonomous abnormalities in insulin signaling. These abnormalities may be triggered by an excess of fatty acids released from visceral adipose tissue into the portal vein, setting off a cascade of events that promote IR [3]. Infiltrating macrophages in adipose tissue and the kidney release inflammatory cytokines, including Interleukin-6 (IL-6) and Tumour Necrosis Factor-Alpha (TNF-α), which worsen IR and contribute to the development of renal impairment [1,4].

Moreover, the complex interaction between obesity and IR also affects the vascular system, particularly endothelial function. Endothelial dysfunction can result from obesity-induced IR, disrupting the balance between the vasodilator Nitric Oxide (NO) and the Reactive Oxygen Species (ROS). It is believed that this widespread vascular endothelial dysfunction and ongoing low-grade inflammation play a role in renal impairment [5]. Microalbuminuria, an indicator of injury to both the renal and systemic vascular beds, can be a manifestation of renal damage [6]. Additionally, IR directly damages the kidneys by causing relaxation of the afferent arteriole, leading to glomerular hyperfiltration, podocyte destruction, and renal damage [1]. Furthermore, IR promotes angiogenesis and mesangial cell growth, further exacerbating nephropathy [1]. These findings highlight the causal relationship between IR, increased adiposity, and renal vascular damage [7]. In order to develop effective therapies, it is crucial to understand the molecular pathways driving IR in obesity. One important mediator in this context is inducible Nitric Oxide Synthase (iNOS), which plays a critical role in increasing IR in skeletal muscle and inhibiting adiponectin release by adipose tissue [8].

The accumulation of intracellular lipid derivatives and the activation of kinases such as Protein Kinase C (PKCs) and c-Jun NH (2)-Terminal Kinase (JNK) are two additional ways in which saturated fatty acids have been linked to the development of IR. These kinases phosphorylate Insulin Receptor Substrate (IRS) serine residues, inhibiting their function and disrupting insulin signaling [9]. It has been hypothesised that the Randle cycle, also known as the Glucose Fatty-Acid cycle, contributes to IR. This metabolic pathway results in impaired glucose utilisation, further exacerbating IR [10]. It also involves competition between glucose and fatty acids for substrates.

Finally, the complex interaction between IR, obesity, and renal impairment is a multifaceted phenomenon. It is crucial to understand the underlying causes of issues including inflammation, endothelial dysfunction, and molecular pathways in order to develop effective defenses against the increasing threat of obesity-related health consequences. To provide comprehensive insights into this crucial health concern, this research explores these mechanisms in more detail by utilising a plethora of scientific data and evidence from relevant publications. The present study was conducted to advance knowledge of these interconnected factors and their effects on

public health by investigating the connections between obesity, IR, and renal impairment.

MATERIALS AND METHODS

This cross-sectional investigation was conducted at the obesity clinic of the endocrinology department in a tertiary hospital. The duration of the study was from February 2014 to May 2015. Ethical clearance was obtained from Amritha Institute of Medical Sciences, kochi Hospital, Kerala, Ethical Committee with IEC Number- Dissertation review/MD/MS/2013/1. Informed consent was obtained from all study participants.

Inclusion criteria:

- Age group: 18 to 65 years
- BMI ≥25.0 km/m^2 for both sexes
- No history of Type 2 Diabetes (T2DM)
- No presence of Red Blood Cells (RBCs), pus cells, or proteinuria in urine (as per standard dipstick urine screening)
- No history of physically demanding activity in the 24 hours prior to the test
- HbA1c <6.5%
- Serum creatinine level of 1.4 mg%.

Exclusion criteria:

- HbA1c ≥6.5%
- Clinical suspicion of urinary tract infection
- Known Cardiovascular Disease (CVD)
- Chronic Kidney Disease (CKD)
- Chronic Liver Disease (CLD)
- Hypertension
- Fever or any other acute or chronic illnesses
- Use of antidiabetic drugs, antiobesity drugs, antihypertensive drugs, nephrotoxic drugs, corticosteroids, and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
- Pregnancy
- Women on birth control pills or in the menstruation phase of the menstrual cycle
- Subjects who were in an upright position for a prolonged duration before the test.

Sample size: Based on results from available literature on two important variables namely UACR and BMI with 95% confidence and 80% power minimum sample size calculated came to be 140.

Data collection: A spot urine sample was collected and placed in a sterile container. The UACR was calculated by determining the ratio of urine albumin (mg/dL) to urine creatinine (g/dL).

Blood sample collection:

- Blood samples were drawn into fluoride-filled vacuum tubes to calculate Fasting Plasma Glucose (FPG). After centrifuging samples at 3000 g for 15 minutes, plasma was transferred to labeled vials.
- Ethylenediamine Tetra Acetic Acid (EDTA) was used as an anticoagulant while collecting blood samples for the HbA1c test in vacuum tubes. The analysis was conducted on whole blood.
- Blood samples without anticoagulant were obtained in vacuum tubes to test various biochemical markers.
- FPG samples were obtained following a 12-hour overnight fast.

Laboratory analysis:

- The Beckman Coulter Olympus AU2700 was used to analyse serum creatinine and FPG.
- A BIO-RAD D-10 analysis of HbA1c was conducted.
- Urine creatinine was determined using Jaffe's kinetic method, and urine albumin estimate was determined using an immunoturbidimetric test.
- The formula (serum insulin (IU/mL) plasma glucose (mg/dL))/ 405 was used to calculate the HOMA-IR using fasting insulin levels. The authors used Chemiluminescent Microparticle Immuno Assay (CMIA) technology to measure plasma insulin levels.

STATISTICAL ANALYSIS

Statistical analysis was performed using International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) Statistics 20.0 for Windows (SPSS Inc., Chicago, USA). The mean values of continuous variables and their related standard deviations were used for summarisation. For normally distributed continuous parameters, the Student's independent samples t-test was used to compare the means between two groups. The Mann-Whitney U test was performed to compare means for parameters that did not have a normal distribution. Pearson's correlation coefficient was used to calculate the correlation between two parameters when both variables had a normal distribution. Spearman's correlation was used to analyse the relationship between non normally distributed parameters. The significance level was set at p-value <0.05. The study's statistical power was set at 80% to ensure sufficient data identification for identifying important links and differences.

RESULTS

The characteristics of the study participants are summarised in [Table/Fig-1], which shows that the majority of the subjects were obese, with an average BMI of 36.78. Additionally, the fact that most patients had HbA1c values around 5.9 indicates successful glycemic management [Table/Fig-2]. The distribution of patients by IR is shown in [Table/Fig-3], demonstrating that a significant majority of participants (83.8%) were classified as having aberrant IR, while only 16.2% had normal IR. This indicates a significant frequency of IR in the study population. [Table/Fig-4] shows the Pearson correlation coefficients, which demonstrate weak relationships between various variables and the UACR.

Particularly, HbA1c (r-value=0.159, p-value=0.056) and IR showed a weak connection with UACR (r-value=0.187, p-value=0.050). Although statistically significant, these correlations merely imply a

Characteristics	n	Mean±SD
Age (years)	144	31.94±11.9
BMI (kg/m^2)	144	36.78±5.15
WC (cm)	144	112.61±10.89
SBP (mmHg)	144	125.35±12.35
DBP (mmHg)	144	78.15±6.64
FPG (mg/dL)	131	98.80±14.75
HBA1c (%)	144	5.64±0.4476
UACR (mg/g)	144	8.49±9.42
Serum creatinine (mg/dL)	143	0.8982±0.1187

[Table/Fig-1]: Baseline characteristics of study participants.
BMI: Body mass index; WC: Waist circumference; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; HbA1c: Hemoglobin A1c; UACR: Urine albumin creatinine ratio

HBA1c (%)	n (%)
Normal <5.9	108 (75)
5.9-6.4	36 (25)
Total	144 (100)

[Table/Fig-2]: Distribution of subjects according to HbA1c.

Variables	Normal %	Abnormal %
FPG (n=131) Normal <106 mgm/dL Abnormal >106 mgm/dL	61.8	38.2
Insulin (n=111) Normal <15 µU/mL Abnormal >15 µU/mL	72.1	27.9
IR (n=111) Normal <2.5 Abnormal >2.5	16.2	83.8

[Table/Fig-3]: Distribution of subjects according to IR.

Factors	n	UACR	
		Pearson correlation	p-value
FPG	131	0.157	0.073
Insulin	111	0.105*	0.274
HBA1c	144	0.159	0.056
IR	111	0.187*	0.050
SBP	144	0.067	0.426
DBP	144	0.090	0.286

[Table/Fig-4]: Pearson's correlations between UACR and metabolic parameters. **Log transformation was done for UACR and variables Insulin and IR due to non-normal distribution and high variation among the observation

tenuous relationship between these factors. [Table/Fig-5] compares participants with normal and abnormal insulin resistance in terms of UACR. In this case, it is clear that UACR was markedly greater among people with aberrant IR, highlighting a possible connection between IR and renal function.

Factor	Classification	n	UACR	p-value
			Mean±SD	
IR	Normal <2.5	18	4.06±2.1	0.013
	Abnormal >2.5	93	9.24±10.33	

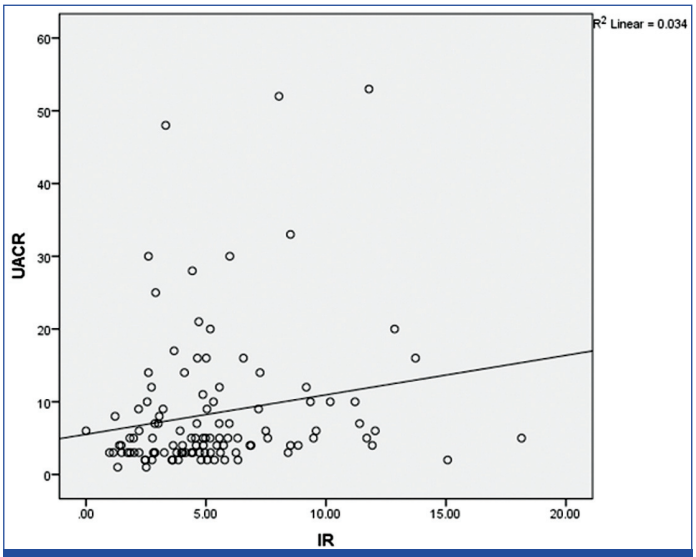
[Table/Fig-5]: Comparison of UACR in IR.
Mann Whitney U test

While there were no significant differences in UACR, fasting insulin, IR, or SBP between the groups, [Table/Fig-6] compares various degrees of obesity and shows that DBP was significantly higher in the severely obese group (BMI >35 kg/m^2). This shows that DBP may be specifically affected by severe obesity. The prevalence of obesity and IR in the research population is highlighted by all these findings. Even though there are statistically significant associations, particularly between insulin resistance, HbA1c, and UACR, their practical applicability may be constrained by the small effect sizes. Nevertheless, the findings highlight the need to track metabolic variables in people with obesity and IR, with an emphasis on glycaemic control and central obesity in particular. Furthermore, the higher DBP seen in patients who are extremely obese, points to the need for thorough cardiovascular risk assessment in this subgroup.

Factor	Classification	n	DBP	p-value
			Mean±SD	
BMI	<35	59	76.68±6.018	0.044
	>35	85	79.18±6.896	

[Table/Fig-6]: Comparison of DBP with BMI.
Mann Whitney U test

The scatter diagram in [Table/Fig-7] emphasises the connection between UACR and IR, as shown in [Table/Fig-4]. Therefore, the findings of this study offer important new understandings of the intricate interactions between obesity, IR, and renal function. Despite the statistical significance of these relationships, further research into their clinical consequences is necessary due to their small effect sizes. These findings nevertheless highlight the significance of careful monitoring of metabolic parameters in people with obesity and insulin resistance, as well as the requirement to take cardiovascular risk factors into account, particularly in cases of severe obesity.



[Table/Fig-7]: Scatter diagram showing the correlation between IR and UACR.

DISCUSSION

In a population with varying degrees of obesity, the current study explores the complex interactions between IR, obesity, and UACR. This study's high incidence of IR (83.8%) among participants showed an elevated HOMA-IR score, a marker of insulin resistance, which is an important finding [Table/Fig-3]. Importantly, this study demonstrated that individuals with IR excrete more urine albumin, as shown by higher UACR levels [Table/Fig-5]. These results are consistent with earlier studies, which highlighted the crucial part played by IR in the pathogenesis of microalbuminuria in the context of obesity [11].

The minor but statistically significant correlations between UACR and variables like IR (r-value=0.187, p-value <0.05) and HbA1c (r-value=0.159, p-value=0.056) are important aspects of this investigation [Table/Fig-4]. Despite the fact that these connections are statistically significant, it is important to note their small sizes. However, this does not lessen their clinical importance, as even slight alterations in renal function can have a significant impact on long-term health.

According to Kim YI et al., type 2 diabetes and hypertension have little impact on the microalbuminuria caused by IR in obese individuals [11]. The study by Anan F et al., further highlighted that the HOMA-IR index functions as an independent predictor of elevated urine albumin excretion [12]. Collectively, the present results show that IR can contribute to renal impairment even in the absence of overt diabetes. Obesity may be considered a significant risk factor for renal impairment since it often underlies IR, especially in the context of chronic hyperinsulinemia [11].

Another important factor to consider in the context of obesity-related renal impairment is inflammation. Adipose tissue functions as an endocrine organ in obesity and releases proinflammatory cytokines that can worsen IR [4]. Additionally, endothelial dysfunction is linked to obesity and can increase IR [5]. According to Lambert E et al., (2010), subclinical organ damage may result from increased sympathetic nervous system activity, which is frequently observed in obesity [13]. These studies highlight the intricate interaction between IR, inflammation, and renal function in the context of obesity.

Further supporting the association between IR and obesity is the Insulin Resistance Atherosclerosis Study conducted by Wagenknecht LE et al., (1995). They found that elevated IR was associated with an increased risk of type 2 diabetes, a condition

closely related to obesity [6]. Importantly, the present study found that Waist Circumference (WC) and Fasting Plasma Glucose (FPG) were both significant predictors of UACR (p-value=0.014 for both WC and FPG) [Table/Fig-4]. This emphasises the importance of these metabolic factors in determining the likelihood of microalbuminuria in the context of IR caused by obesity.

The connection between IR, obesity, and renal impairment may be explained by several molecular pathways. One such mechanism is the effect of fatty acids on mitochondrial activity, which can lead to IR, as proposed by Martins AR et al., [14]. Furthermore, cytokines, especially those produced by adipose tissue, can influence glucose transport and promote IR [8]. The Randle cycle, which controls how lipids and carbohydrates interact, might also be involved in IR [10]. Metabolic syndrome and IR have been linked to visceral adiposity, which is typically seen in obese individuals [15]. These pathways demonstrate how intricately IR, obesity, and renal function interact with each other.

Although this study provides insight into the connection between insulin resistance, obesity, and renal function, it is important to recognise both its weaknesses and advantages. One notable advantage is the thorough evaluation of several metabolic markers and their relationships to UACR. This approach provides valuable information on the complex nature of the relationship under investigation. Additionally, the large sample size improves the study's statistical power, enabling the identification of minor relationships [11,12].

The importance of assessing renal health in individuals with obesity and IR is highlighted by this study, which also sheds light on possible relationships between microalbuminuria, HbA1c, and other variables [5,16]. These results suggest that obese populations should undergo early screening procedures, such as microalbuminuria and HbA1c evaluations, to prevent kidney impairment. The report also emphasises the crucial role of governments and healthcare practitioners in translating research evidence into practice. It underscores the intricate connection between metabolic variables and renal function in obesity and IR and calls for further research to investigate the underlying mechanisms and establish causality.

Limitation(s)

However, there are a few limitations to consider. Firstly, the study's cross-sectional design makes it impossible to establish a causal link between microalbuminuria, obesity, and insulin resistance. Longitudinal research would be helpful to clarify the temporal correlations between these components [17]. Secondly, the study population includes individuals with varying degrees of obesity, which increases variability. More detailed insights could be gained through stratified analysis or subgroup studies based on the severity of obesity [18]. Finally, it is possible that other variables not considered in this study may have an impact on renal function, given the very small effect sizes observed in the correlations between various variables and UACR [14].

CONCLUSION(S)

The results of this study highlight the strong correlation between UACR and IR in obese individuals. The higher UACR values in individuals with IR indicate the possibility of early signs of renal failure in this cohort. Monitoring these variables should be a key component of healthcare interventions for obese individuals, given the weak connections between UACR and both IR and HbA1c. Obesity is becoming increasingly prevalent worldwide, and its association with Chronic Kidney Disease (CKD) has significant public health implications. It is crucial to translate the evidence generated from obesity research into knowledge that healthcare practitioners and policymakers can utilise. A critical first step in preventing renal injury and its associated problems could be the early detection of microalbuminuria and high blood sugar levels in all obese individuals. Future studies should investigate the underlying pathways linking obesity, IR, and renal function to further advance this field of study. To establish causation and gain a better understanding of the course of renal impairment in obese individuals, longitudinal studies are required. Additionally, future research and healthcare policies should focus on therapies and strategies to manage insulin resistance and prevent or mitigate kidney impairment. Therefore, this study emphasises the importance of considering obesity, insulin resistance, and renal function. The findings highlight the potential for early intervention through consistent UACR and HbA1c monitoring, providing an opportunity to mitigate the effects of renal failure in this high-risk population. By being proactive and implementing tailored therapies, the clinicians can strive to reduce the burden of chronic kidney disease in individuals with obesity and insulin resistance.

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