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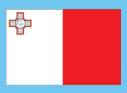

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OBSERVATION

Glycemia management in critical care patients

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Abstract

Over the last decade, the approach to clinical management of blood glucose concentration (BGC) in critical care patients has dramatically changed. In this editorial, the risks related to hypo, hyperglycemia and high BGC variability, optimal BGC target range and BGC monitoring devices for patients in the intensive care unit (ICU) will be discussed. Hypoglycemia has an increased risk of death, even after the occurrence of a single episode of mild hypoglycemia (BGC < 80 mg/dL), and it is also associated with an increase in the ICU length of stay, the major determinant of ICU costs. Hyperglycemia (with a threshold value of 180 mg/dL) is associated with an increased risk of death, longer length of stay and higher infective morbidity in ICU patients. In ICU patients, insulin infusion aimed at maintaining BGC within a 140-180 mg/dL target range (NICE-SUGAR protocol) is considered to be the state-of-the-art. Recent evidence suggests that a lower BGC target range (129-145 mg/dL) is safe and associated with lower mortality. In trauma patients without traumatic brain injury, tight BGC (target < 110 mg/dL) might be associated with lower mortality. Safe BGC targeting and estimation of optimal insulin dose titration should include an adequate nutrition protocol, the length of insulin infusion and the change in insulin sensitivity over time. Continuous glucose monitoring devices that provide accurate measurement can contribute to minimizing the risk of hypoglycemia and improve insulin titration. In conclusion, in ICU patients, safe and effective glycemia management is based on accurate glycemia monitoring and achievement of the optimal BGC target range by using insulin titration, along with an adequate nutritional protocol.

Key words: Glycemia management; Intensive insulin therapy; Hyperglycemia; Hypoglycemia; Metabolism; Intensive care

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INTRODUCTION

Over the last decade, the approach to clinical management of blood glucose concentration (BGC) in critical care patients has dramatically changed. Traditionally, BGC management in patients admitted to intensive care units (ICU) was mostly overlooked and "permissive" hyperglycemia was the standard of care[1,2]. In 2001, Van den Berghe *et al*[3] published the results of an innovative approach that tested a more aggressive management and proposed intensive insulin infusion therapy (IIT) targeted to tight BGC control (80-110 mg/dL). A few years later, it became clear that this approach carries the risk of increased frequency of hypoglycemia[4-6]. Subsequently, the

NICE-SUGAR study has demonstrated that moderate BGC control (140-180 mg/dL) is associated with lower mortality and a lower risk of hypoglycemia when compared to tight BGC[7].

In this editorial, the risks related to hypo, hyperglycemia and high BGC variability, optimal BGC target range and BGC monitoring devices for patients in ICU will be discussed.

RISKS RELATED TO HYPOGLYCEMIA

Hypoglycemia is related to an increased risk of death, even after a single episode of mild hypoglycemia occurs, and to an increase in ICU length of stay (LOS) (Table 1). In an observational study of 4946 ICU patients treated with moderate BGC control (target BGC range 108-180 mg/dL), at least 1 episode of hypoglycemia (BGC < 81 mg/dL) in 1109 patients was recorded[8]. In this study group, patients that developed hypoglycemia were at higher risk for mortality compared to those who did not (death 36.6% *vs* 19.7%, $P < 0.05$). It is important to underscore that even episodes of mild hypoglycemia (BGC 72-81 mg/dL) were associated with higher hospital mortality: 25.9% *vs* 19.7%, $P < 0.05$.

In a retrospective analysis of prospectively collected data in 6240 patients admitted to ICU, focused on the association between hypoglycemia (defined as BGC < 70 mg/dL) and LOS, these variables were consistently related, with dose-response and episode-based having a linear predictive value[9]. In patients without hypoglycemia compared to those with a single episode, ICU median interquartile LOS was 1.8 (1-0-3.3) *vs* 3.0 (1.5-6.7) d, $P < 0.0001$. The relationship between hypoglycemia and LOS was independent of the severity of illness and survivor status. The authors concluded: "Successful avoidance of hypoglycemia has the potential to significantly decrease the cost of care of the critically ill". The LOS is the predominant measure of resource utilization in critical care patients. Various studies have provided evidence on costs savings related to preventing hyperglycemia because of decreased LOS, infections, pharmacy, laboratory and imaging use[10]. Also, the prevention of hypoglycemia can contribute to the reduction of LOS and ICU costs.

RISKS RELATED TO HYPERGLYCEMIA

Hyperglycemia, with a threshold value of 180 mg/dL, relates to an increased risk of death, LOS and morbidity due to infection in ICU patients. In a retrospective chart review of 210 patients assigned to moderate BGC control (target range 80-140 mg/dL) or with an uncontrolled BGC regimen, patients assigned to the latter group treatment had a higher mortality (5% *vs* 18%, $P < 0.01$)[11,12]. Mean BGC values higher than 181 mg/dL were associated with an increased risk of death: OR = 1.3, 95% CI: 1.1-1.6; $P = 0.01$. The increased mortality related to hyperglycemia is confirmed by data on BGC at ICU admission in 5828 medical/surgical ICU patients[13].

Table 1 Risks related to hypo, hyper glycemia and high blood glucose target range variability

Take home message
Hypoglycemia is clinically relevant, increased mortality and LOS for BGC values < 80 mg/dL
The risk of hypoglycemic episodes is related to: BGC target range; insulin infusion duration
Hyperglycemia is clinically relevant, increased mortality, increased LOS and higher incidence of postoperative infections for BGC values > 181 mg/dL
High glycemia variability and high complexity of glycemic profile are associated with increased mortality rate

BGC: Blood glucose concentration; LOS: Length of stay.

In this study, cohort data were divided into quintiles of increasing mean BGC and the results demonstrated that mean BGC at ICU admission is related to mortality by a "U-shaped" curve, values < 120 mg/dL and > 162 mg/dL were associated with increased risk of death: OR 2.4 (1.4-4.0) and 3.0 (1.8-5.1); $P < 0.001$.

A similar trend, with "U-shaped" relationship links mean glucose concentration during the first 24 h after surgery and the incidence of postoperative infections, as reported in a retrospective analysis of a sample of 55 408 diabetic patients that underwent non cardiac procedures[14]. In those patients with a mean 24 h serum glucose 150 to 250 mg/dL, the incidence rate ratio was 1.22, 95% CI: 1.04-1.43, $P = 0.01$. Of interest, in this study group the values of preoperative serum glucose concentration and hemoglobin A1c were not associated with an increased risk of postoperative infections, suggesting that was not the quality of preoperative glycemia control that determined the increase in infection rate.

RISKS RELATED TO HIGH BGC VARIABILITY

High serum glucose variability and differences in complexity of the glycemic profile predicts increased risk of death in ICU patients.

Risk related to BGC variability as a predictor of mortality in an ICU population was initially presented by Krinsley and demonstrated how standard deviation (SD) within different ranges of mean glycemia is associated with increased death rate[15]. However, SD is not the most appropriate statistical approach to measure the extent of BGC variability[16]. In a retrospective analysis in 5728 ICU patients, treated with a computerized-based sliding-scale IIT targeted to BGC 72-126 mg/dL target range, the mean absolute glucose change (MAG) per patient per hour (that is a function of BGC absolute changes and time spent in ICU) was associated with ICU death in the low and high ranges of BGC: OR 4.1, 95% CI: 1.9-9.1; $P < 0.001$[17]. The MAG values were more tightly associated with mortality rate than SD of median BGC; median SD was 32 mg/dL and median MAG was 11 mg/dL; thus

qualifying this approach to evaluate changes in glycemia variability. Results from this study have also further demonstrated how hyperglycemia is harmful, since when high MAG was associated with high mean BGC (highest quartile), the highest mortality rate was recorded: OR 12.4, 95% CI: 3.2-47.9; $P = 0.001$. This evidence was confirmed in a prospective study in 48 ICU patients where a continuous measure of subcutaneous interstitial fluid glucose levels were recorded every 5 min for 48 h[18]. In these patients, the complexity of glycemic profile was evaluated by detrended fluctuation analysis (DFA) and resulted in significantly lower values in survivors compared to non-survivors: 1.49 (CI: 1.44-1.53) *vs* 1.60, $P = 0.015$. Of interest in this study, patients age, gender, simplified acute physiological score 3 and Acute Physiology and Chronic Health Evaluation Ⅱ scores, type of feeding (oral, enteral or parenteral) and amount of insulin infused were not associated with differences in DFA.

According to this evidence, it is important to minimize sudden changes in BGC and therefore to avoid insulin bolus injections, both intravenous and subcutaneous, and to prevent the infusion of solutions containing high glucose concentration that are sometimes prescribed to correct iatrogenic induced hypoglycemia.

OPTIMAL BGC TARGET RANGE

Over time the optimal BGC target range has dramatically changed[19]. Available evidence now suggests that a tailored BGC target range should be adopted in specific subgroups of patients and might be corrected according to the nutrition protocol used and depending on the duration of insulin infusion. According to the NICE-SUGAR data results, as mentioned in the introduction section, there is no additional benefit from lowering BGC levels below a "moderate" target range (140-180 mg/dL); this range is associated with lower 90 d mortality compared to "tight" BGC (target range 80-110 mg/dL) and to a lower risk of severe hypoglycemia.

This evidence was in part challenged by 2 retrospective reviews that analyzed data in trauma patients. In 2008, patients survival rate before and after the implementation of tight BGC control protocol (standard BGC target range 80-200 mg/dL *vs* tight BGC target range 80-110 mg/dL) resulted into a significant improvement in those aged 41 to 50 years and 51 to 60 years: 21/131 (18.3%) *vs* 20/226 (8.8%); $P = 0.009$ and 24/86 (27.9%) *vs* 26/181 14.4%; $P = 0.08$[20]. Data from 1422 trauma patients when retrospectively divided into 3 non-overlapping, sequential treatment groups according to the protocol used for BGC control (relaxed: BGC target range <180 mg/dL; aggressive: BGC target range 80-120 mg/dL; and moderate: BGC target range 80-140 mg/dL), demonstrated that a "moderate" approach balanced maintenance of normoglycemia, reduction in glucose variability and minimization of hypoglycemic and hyperglycemic events, while maintaining equivalent outcomes when compared with a more aggressive strategy[21]. This study also confirmed that hyperglycemic events (BGC > 180 mg/dL) most strongly predicted mortality. The optimal BGC target range is not yet established and the authors of this study commented: "Additional rigorous studies would be needed to identify the specific normoglycemic ranges and protocol adjustment and monitoring characteristics required to achieve target glucose level". In a prospective nested cohort study in 523 medical/surgical ICU patients assigned to 1 out of 6 BGC target range group treatments (group1 BCG < 108 mg/dL; group 2 BGC 108-114 mg/dL; group 3 BGC 115-128 mg/dL; group 4 BGC 129-145 mg/dL; groups 5 BGC 146-181 mg/dL; group 6 BGC > 181 mg/dL), the 129-145 mg/dL target range was associated with the lowest mortality rate[22]. The authors concluded that targeting BGC to < 146 mg/dL ("advanced BGC target range: 129-145 mg/dL) is associated with less risk of inadvertent hypoglycemia and represents an optimal BGC level in critically ill patients.

The target BGC level is not the only variable that affects the relationship between insulin infusion, the risk of iatrogenic hypoglycemia and ICU outcome. Among the most relevant variables that contribute to determine the effects of insulin infusion on BGC are: the nutritional protocol, duration of insulin infusion and the changes in insulin sensitivity over time.

A systematic review and meta analysis of the effects of tight BGC control (80-110 mg/dL) in ICU patients showed that this approach does not reduce 28 d hospital mortality, incidence of blood stream infections or requirement for renal replacement therapy[23]. The authors also recorded that IIT may be harmful in patients receiving enteral nutrition; however, it appears to improve the outcome of patients receiving the majority of their carbohydrate load parenterally. The duration of insulin infusion is a predictor of severe hypoglycemia (BGC < 40 mg/dL), as demonstrated in a retrospective analysis in 1118 ICU surgical patients treated with tight BGC (target BGC 80-110 mg/dL)[24]. This study confirmed the increased odds for death among patients even after a single episode of hypoglycemia (26.9% *vs* 15.3%, $P = 0.03$) and showed how occurrence of severe hypoglycemia does not reflect illness severity or demographic features but is related to the time of insulin infusion. The relationship of length of insulin infusion can be possibly explained by the induced changes in insulin sensitivity.

According to available evidence, state-of-the-art BGC management in ICU patients should be addressed to maintain glycemia within 140-180 mg/dL target range (NICE-SUGAR). More recent evidence suggests that a lower target range 129-145 mg/dL is associated with the lowest mortality rate as compared to other treatment groups. In some subgroups of patients, "dedicated" target ranges might have clinical benefits. In trauma patients without traumatic brain injury[25], "moderate" BGC management (BGC target range 80-140 mg/dL) or "tight" BGC management (BGC target range 80-110 mg/dL) in the 41-60 year age group is associated with reduced

mortality. Safe BGC targeting and estimation of optimal insulin dose titration should include an adequate nutrition protocol, the length of insulin infusion and the change in insulin sensitivity over time.

BGC MONITORING

Critical care control of BGC necessitates frequent and accurate monitoring to avoid hypoglycemia and inadequate insulin titration[26]. Traditionally, clinical glucose measurements are based on central laboratory devices and point of care (POC) devices. The POC devices, although potentially attractive because of ease of handling and rapid results, are not suitable in ICU patients due to inaccuracy (differences in results exceeding 20% of a reference value)[26]. Besides issues related to POC device accuracy, it is important to recall that several clinical and laboratory variables, including inadequate cardiac output, arterial hypotension, hypoxia, hematocrit values, pH, associated therapies etc., can interfere with BGC measurement accuracy[26,27]. These issues have driven the need for real time continuous glucose monitoring (CGM) devices[28]. Recently, an intravascular CGM sensor has been tested in the preclinical setting with promising results[29,30]. The CGM can possibly contribute, not only to minimizing the risk of hypoglycemic events and to optimize insulin titration, but also to provide information on BGC variability and trends. These variables are possible predictors of outcome in ICU patients[31].

CONCLUSION

In critical care patients, hypo, hyper and high BGC variability are associated with an increased risk of death. The relationship between mean BGC and mortality is described by a "U-shaped" curve, with lower and higher BGC values associated with higher death rate. Similarly, increased rates of BGC variability and complexity of glycemic profiles relates to higher ICU mortality.

It is clinically relevant to underline that even mild hypoglycemia (BGC < 80 mg/dL) is associated with an increased risk of death; this value should therefore be considered the lower threshold for safe BGC management in ICU patients. The higher glycemia threshold is 180 mg/dL; values that exceed this level are associated with increased morbidity and mortality. Preventing hypoglycemia and hyperglycemia can also effectively contribute to reduce LOS and ICU costs. As much attention that is spent to prevent hypo and hyper glycemia should be used to minimize changes in BGC variability. Therefore, bolus insulin injection, both intravenous and subcutaneous, and bolus infusion of high glucose concentration solutions should be strictly avoided (Table 2).

State-of-the-art for glucose target range encompasses insulin infusions aimed at maintaining BGC within 140-180 mg/dL range. Recent evidence suggests that lower BGC target range (129-145 mg/dL) is safe and effective in ICU patients. In trauma patients without traumatic brain injury, moderate BGC (target < 140 mg/dL) is associated with reduced mortality.

Table 2 Practical tips for blood concentration

Take home message
Avoid injecting insulin boluses, both subcutaneous and intravenous
Avoid infusing high glucose concentration solution
Avoid point of care devices for BGC measurements
Use parenteral nutrition
In ICU patients
"Standard", according to the "state-of-the-art" BGC target range: 140-180 mg/dL
"Advanced" BGC target range: 129-145 mg/dL
In trauma patients (without traumatic brain injury):
Overall: BGC < 140 mg/dL
If aged 41-60 years: 80-110 mg/dL

BGC: Blood glucose concentration; ICU: Intensive care unit

Continuous glucose monitoring devices that provide accurate measurement can contribute to minimizing the risk of hypoglycemia and improving insulin titration.

In conclusion, in ICU, a patient's safe and effective glycemia management is based on accurate glycemia monitoring, achieving optimal BGC target range and insulin titration, along with an adequate nutritional protocol.

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ORIGINAL ARTICLE

Over expression of resistin in adipose tissue of the obese induces insulin resistance

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Abstract

AIM: To compare resistin mRNA expression in subcutaneous adipose tissue (SAT) and its correlation with insulin resistance (IR) in postmenopausal obese women.

METHODS: A total of 68 postmenopausal women (non obese = 34 and obese = 34) were enrolled for the study. The women of the two groups were age matched (49-70 years). Fasting blood samples were collected at admission and abdominal SAT was obtained during surgery for gall bladder stones or hysterectomy. Physical parameters [age, height, weight, body mass index (BMI)] were measured. Biochemical (plasma insulin and plasma glucose) parameters were estimated by enzymatic methods. RNA was isolated by the Trizol method. SAT resistin mRNA expression was done by real time-reverse transcription polymerase chain reaction (RT-PCR) by using Quanti Tect SYBR Green RT-PCR master mix. Data was analyzed using independent Student's *t* test, correlation and simple linear regression analysis.

RESULTS: The mean weight (52.81 ± 8.04 kg *vs* 79.56 ± 9.91 kg; $P < 0.001$), BMI (20.23 ± 3.05 kg/m^2 *vs* 32.19 ± 4.86 kg/m^2; $P < 0.001$), insulin (8.47 ± 3.24 μU/mL *vs* 14.67 ± 2.18 μU/mL; $P < 0.001$), glucose (97.44 ± 11.31 mg/dL *vs* 109.67 ± 8.02 mg/dL; $P < 0.001$) and homeostasis model assessment index (2.01 ± 0.73 *vs* 3.96 ± 0.61; $P < 0.001$) were significantly higher in postmenopausal obese women compared to postmenopausal non obese women. The mean serum resistin level was also significantly higher in postmenopausal obese women compared to postmenopausal non obese women (9.05 ± 5.15 *vs* 13.92 ± 6.32, $P < 0.001$). Furthermore, the mean SAT resistin mRNA expression was also significantly (0.023 ± 0.008 *vs* 0.036 ± 0.009; $P < 0.001$) higher and over expressed 1.62 fold (up-regulated) in postmenopausal obese women compared to postmenopausal non obese women. In postmenopausal obese women, the relative SAT resistin mRNA expression showed positive (direct) and significant correlation with BMI ($r = 0.78$, $P < 0.001$) and serum resistin ($r = 0.76$, $P < 0.001$). Furthermore, the SAT resistin mRNA expression in postmenopausal obese women also showed significant and direct association ($r = 0.45$, $P < 0.01$) with IR, while in postmenopausal non obese women it did not show any association ($r = -0.04$, $P > 0.05$).

CONCLUSION: Increased SAT resistin mRNA expression probably leads to inducing insulin resistance and thus may be associated with obesity-related disorders in postmenopausal obese women.

Key words: Resistin; Subcutaneous adipose tissue; Insu-

lin resistance; Obesity; Body mass index

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INTRODUCTION

Obesity is one of the most common metabolic disorders in developing countries and is characterized by a reduction in insulin sensitivity, both in animal models and in humans[1]. The incidence of obesity worldwide has increased drastically during recent decades. Consequently, obesity and associated disorders now constitute a serious threat to the current and future health of the population. The World Health Organization (WHO) estimates that more than 1 billion adults worldwide are overweight, 300 million of whom are clinically obese, defined as having a body mass index (BMI) equal to or greater than 30 kg/m^2[2]. Obesity is associated with an array of additional health problems, including increased risk of insulin resistance, type 2 diabetes (T2D), fatty liver disease, atherosclerosis, degenerative disorders including dementia, airway disease and some cancers[3]. The molecular mechanisms involved in obesity-related insulin resistance are not yet well understood.

Postmenopausal obese women may be at increased risk for metabolic syndrome (MetS) because of the increase in total and central adiposity after menopause transition[4]. The emergence of these risk factors may be a direct result of ovarian failure or alternatively an indirect result of metabolic consequences of central fat redistribution with estrogen deficiency[5]. Adipose tissue is an active metabolic tissue that secretes multiple metabolically important proteins known as "adipokines" (leptin, adiponectin, tumor necrosis factor (TNF)-α, interleukin (IL)-6 and resistin *etc.*)[6,7]. These adipocyte derived products are presently subject to intensive research concerning their involvement in the regulation of adipose tissue physiology and in particular their potential implication in insulin resistance (IR), obesity and diabetes[8,9].

Plasma concentration of resistin is elevated in obesity compared to a healthy person. In humans and rodents, plasma resistin concentrations are positively correlated with BMI[10]. It is well documented that accumulation of visceral fat is associated with a higher risk for development of obesity-related diseases such as T2D, cardiovascular disease, hypertension and hyperlipidemia[11,12]. However, the role of subcutaneous adipose tissue (SAT) dysregulation could be a potential mechanism but its role in the pathogenesis of MetS has been conflicting[13]. The SAT, which comprises approximately 80% of adipose tissue and the major source of fatty acids for the liver, has metabolically correlated to indices of insulin resistance as well as to visceral adipose tissue (VAT)[14-17].

In addition to intra-abdominal fat, Salmenniemi *et al*[18] have shown that the amount of SAT in subjects with MetS positively correlates with increasing MetS and negatively correlates with circulating adiponectin levels. Carr *et al*[19] have also reported that SAT is significantly associated with MetS and increases with increasing number of MetS features, independent of age and sex.

Several studies have shown that both VAT and SAT are associated with adverse cardio metabolic risk factors[20,21]. Regardless of these observations and continuing debate regarding metabolic importance of VAT and SAT, it appears that both contribute significantly to metabolic and cardiovascular risks. However, due to higher mass of SAT than VAT, it may affect metabolic factors more significantly[22] and thus may have more clinical importance. Furthermore, subcutaneous adipocytes are larger than omental, have higher lipoprotein lipase activity and are more lipolytic on an absolute basis, which reflect a higher fat storage capacity in this depot, especially in women[23].

Recently, a significant link between SAT and dyslipidemia in patients with T2D was reported[24]. Visceral and subcutaneous adipocytes have different capacities to produce hormones and enzymes with variation in mRNA expressions of adipokines (resistin, adiponectin, TNF-α, IL-6 *etc.*) from various depots of adipose tissue[25].

In an animal study, expression of resistin in subcutaneous adipose tissue was controversial[26]. In humans, data on resistin is conflicting. Some authors have shown that it is elevated in individuals with obesity and diabetes[27-29], whereas others have shown that it is not elevated[30-32]. A recent study reported that human resistin induced insulin resistance and Metformin reversed the effect of resistin in hepatocytes[33]. Taken together, these studies suggest that the depot-specific expression of resistin at the mRNA level could be relevant to insulin sensitivity.

The literature regarding the SAT resistin expression in Asian populations, especially Indians, is lacking. Thus, with best our knowledge, the present study was undertaken with the objective to investigate SAT resistin mRNA expression in postmenopausal Indian women and its association with insulin resistance.

MATERIALS AND METHODS

Subjects

A total of 68 postmenopausal (non obese = 34 and obese = 34) age matched (49-70 years) women were recruited at CSM Medical University, Lucknow, India who underwent elective abdominal surgery for gall bladder stones or hysterectomy. Respective abdominal SAT was obtained during the surgery. During surgery, no specific standard diet and hormonal therapy were given to the patients, which ensured and ruled out the effect of hormones or diet on fat deposition. All tissue samples were stored in RNAlatar (Sigma-Aldrich) for RNA extraction. The study was approved by the Institutional Ethics Committee. Subjects

were classified as obese according to BMI > 25 kg/m^2, as per WHO's guideline for Asians[34], and BMI < 25 kg/m^2 as non obese served as control. Informed consent was obtained from each patient.

Biochemical estimation

Blood samples were taken the morning after their admission to the hospital for surgery. Plasma insulin concentrations were determined using immune radiometric assay (immunotech). Plasma glucose concentrations were determined by glucose oxidase-peroxidase method (Merck) using semi automated glucose analyzer (Microlab 300, Merck). Serum resistin level was measured by enzyme-linked immunosorbent assay (Quantikine Human Resistin Version 16 190607 15, Biovendor).

Calculation: Insulin resistance

Homeostasis model assessment (HOMA), an index of IR[35] based on plasma levels of fasting glucose and insulin, has been widely applied for quantifying insulin resistance and β-cell function in an Asian population was evaluated as [HOMA-IR = fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5].

RNA extraction

Total RNA was isolated using Tri-Reagent (Sigma Chemical Co., St. Louis, MO). RNA was measured spectrophotometrically at 260 and 280 nm, while RNA integrity was checked by visual inspection of the two ribosomal RNAs 18S and 28S on agarose gel.

Real-time polymerase chain reaction measurement of resistin mRNA

One-step reverse transcription polymerase chain reaction (RT-PCR) was carried out using Quanti Tect SYBR Green RT-PCR master mix kit (Qiagen). PCR amplification was carried out in Light Cycler 480 (Roche, real time thermal cycler). Ninety-six well PCR plate using following temperature profile of 50 ℃, 30 min, (Reverse transcription) 95 ℃, 15 min, (initial denaturation) followed by 40 cycles of 94 ℃, 15 s, 59 ℃, 30 s and 72 ℃, 30 s for denaturation, annealing and extension steps respectively. Primer sequence of human resistin was 5'-GCTGTTG-GTGTCTAGCAAGAC-3' (forward) 5'-CATCATCAT-CATCATCTCCAG-3' (reverse). The following primer sequence of β-actin as internal control with following sequence was 5'-GTGGCATCCACGAAACTACCTT-3' (forward) and 5'-GGACTCCTGATACTCCTGCTTG-3' (reverse). The PCR primers were synthesized by Agile Life Science Technologies India. Expression of glyceraldehyde-3-phosphate dehydrogenase or β-actin was used to normalize resistin expression values. There was no difference in glyceraldehyde-3-phosphate dehydrogenase or β-actin expression between adipocytes from non obese and obese subjects or between the omental and subcutaneous depots.

Statistical analysis

Data were expressed as mean ± SD. Anthropometric measurements and biochemical parameters and SAT resistin mRNA expression of the two independent groups were compared by Student's *t* test. Correlation and simple linear regression analysis was done to assess association of resistin SAT mRNA expressions with BMI and HOMA index, considering BMI and HOMA index an independent variable and SAT resistin mRNA expression, the dependent variable. A two-sided ($a = 2$) conventional $P < 0.05$ was considered statistically significant.

RESULTS

Basic characteristics

The basic characteristics viz. physical (age, weight, height and BMI) and biochemical parameters (insulin, glucose and HOMA index) of the two groups are summarized in Table 1. Table 1 shows that the mean weight, BMI, insulin, glucose and HOMA index were significantly ($P < 0.001$) higher in the obese compared to non obese. However, the age and height were found to be similar ($P > 0.05$) between the two groups, indicating the subjects of two groups were age matched.

Table 1 Physical and biochemical parameters summary (mean ± SD) of two groups ($n = 34$)

Variables	Non obese	Obese	*P* value
Age (yr)	54.94 ± 6.87	54.06 ± 6.71	0.594
Weight (kg)	52.81 ± 8.04	79.56 ± 9.91	< 0.001
Height (cm)	161.76 ± 8.17	157.74 ± 9.09	0.059
BMI (kg/m^2)	20.23 ± 3.05	32.19 ± 4.86	< 0.001
Insulin (μU/mL)	8.47 ± 3.24	14.67 ± 2.18	< 0.001
Glucose (mg/dL)	97.44 ± 11.31	109.67 ± 8.02	< 0.001
HOMA	2.01 ± 0.73	3.96 ± 0.61	< 0.001

BMI: Body mass index; HOMA: Homeostasis model assessment.

Resistin mRNA expression in SAT

The SAT resistin mRNA expression of non obese and obese is summarized graphically in Figure 1. Figure 1 shows that the mean SAT resistin mRNA expression of obese was significantly higher compared to non obese (0.023 ± 0.008 *vs* 0.036 ± 0.009, $P < 0.001$). The relative mean SAT resistin mRNA expression up regulated 1.62 fold (56.1%) in the obese than non obese. Furthermore, mean serum resistin level were also significantly higher in obese compared to non obese (9.05 ± 5.15 *vs* 13.92 ± 6.32, $P < 0.001$) (Figure 2).

Correlations of resistin mRNA expression with BMI, serum resistin and insulin resistance

The association of relative SAT resistin mRNA expression of obese women with their respective BMI, serum resistin and insulin resistance (HOMA) are shown graphically in Figure 3. Figure 3 shows that the relative SAT

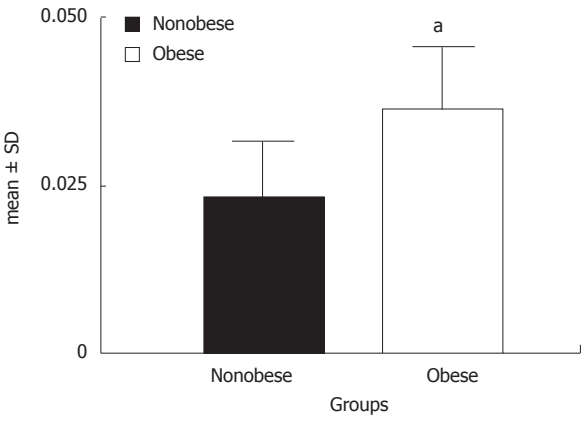

Figure 1 Relative subcutaneous adipose tissue resistin mRNA expressions of two groups. [a]$P < 0.001$ *vs* non obese (by Student's *t* test).

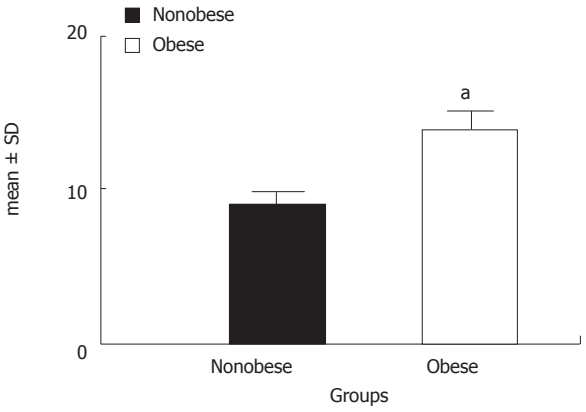

Figure 2 Mean serum resistin levels (ng/mL) of two groups. [a]$P < 0.001$ *vs* non obese (by Student's *t* test).

resistin mRNA expression positively (directly) and significantly correlated with BMI ($r = 0.78$, $P < 0.001$), HOMA ($r = 0.45$, $P < 0.01$) and serum resistin ($r = 0.76$, $P < 0.001$).

DISCUSSION

The physiological functions of resistin in humans have been mostly investigated at the levels of DNA polymorphisms and plasma proteins[36,37]. However, only a few studies have tried to relate the resistin mRNA levels to some physiological functions, such as obesity, diabetes and insulin sensitivity[29,38]. Furthermore, most of the mRNA studies consist of small sample sizes with controversial findings. Although the limitation of sample size prevented these mRNA reports from more comprehensive analyses compared with those studies using plasma resistin, the value of these studies should not be overlooked.

The literature regarding SAT resistin mRNA expression in Asians, especially Indians, is lacking. With the best of our knowledge, for the first time, the present study evaluates SAT resistin mRNA expression in postmenopausal Indian women and its association with insulin resistance. In the present study, we found significantly

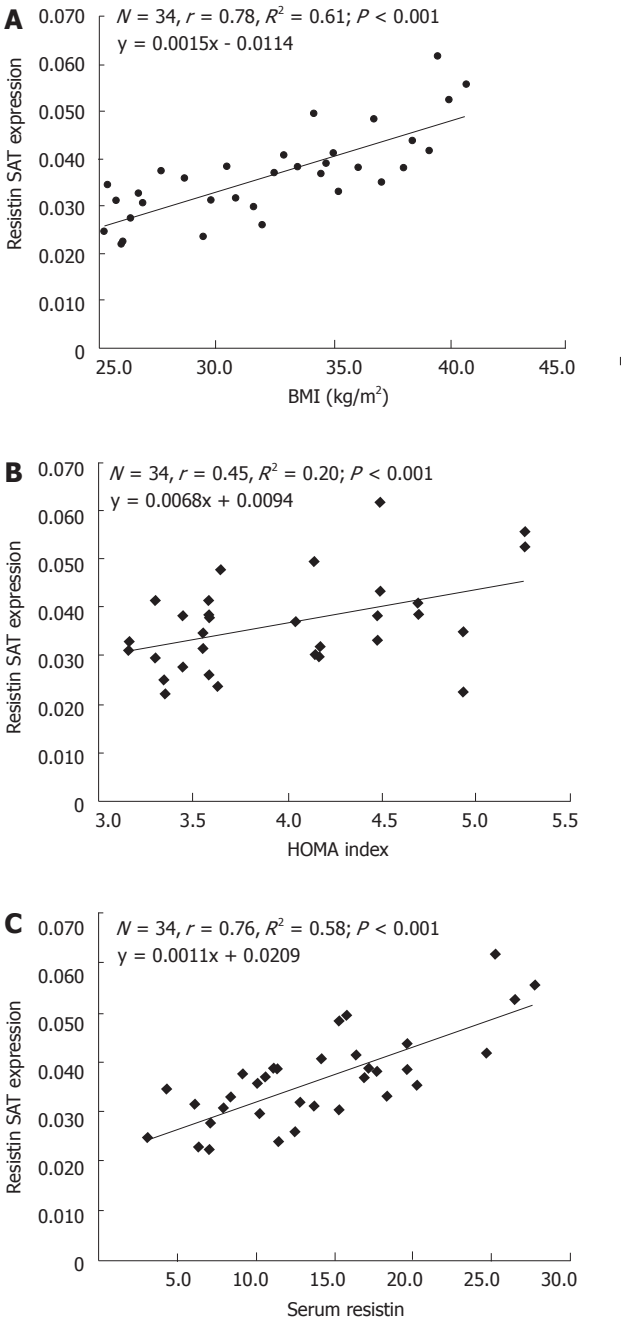

Figure 3 Correlation and simple linear regression of subcutaneous adipose tissue resistin mRNA expression with body mass index (A), homeostasis model assessment index (B) and serum resistin levels (C) in postmenopausal obese women. HOMA: Homeostasis model assessment; BMI: Body mass index.

higher SAT resistin mRNA expression in the obese compared to non obese. Our finding is in contrast with Baranova *et al*[39] who reported no difference in SAT resistin mRNA expression in the obese with and without insulin resistance. However, a few reports show decreased mRNA and protein expression in isolated subcutaneous and omental adipocytes[40,41].

Findings of resistin gene expression in humans are controversial. Some reports have shown mRNA or protein expression in human adipose tissue, while others

have reported the absence/poor mRNA expression in this tissue[42,43]. Our findings corroborate with a cohort study by Smith *et al*[37] who reported higher expression in obese women. Moreover, a recent report showed higher resistin mRNA expression of both visceral and subcutaneous adipose tissues in obese than non obese women[25].

It was also shown that serum resistin had significant effects on insulin action, potentially linking obesity with IR[44]. Previous studies examined showed that serum resistin concentrations are raised in high-fat-induced obese and obese mice models[45]. It is well documented that administration of anti resistin antibody improves insulin action and glucose metabolism in mice with diet-induced obesity, suggesting a role for resistin in the development of insulin resistance[45]. In addition, a recent study showed that administration of recombinant resistin causes insulin resistance in mice[46]. It is also well documented that resistin decreases insulin-stimulated glucose uptake in 3T3-L1 adipocytes and the inhibitory effect is prevented by anti resistin antibody[45]. These findings strengthen the hypothesis that resistin may be a link between obesity and its associated risks.

In the present study, we also determined the level of serum resistin in obese and non obese postmenopausal women. Serum resistin was significantly higher in the obese than non obese. Our finding is in accordance with Degawan *et al*[29] who reported significantly higher resistin protein in the serum of obese than non obese. However, several studies showed that serum resistin level do not correlate well with markers of adiposity[8,31]. Savage *et al*[40] also reported no correlation between insulin resistance and resistin gene expression in whole abdominal adipose tissue. In contrast, we found positive and significant correlation of SAT resistin mRNA expression with BMI, HOMA and serum resistin levels in obese women. The finding is consistent with a recent finding which showed a strong correlation between serum resistin and resistin mRNA expression of abdominal SAT in the obese[30]. However, Yang *et al*[38] reported that resistin was undetectable in SAT and unrelated to insulin resistance. One study[29] reported higher SAT resistin expression in the obese and positive association with BMI but not related to insulin resistance. We hypothesized that the conflicting results regarding SAT resistin mRNA expression in humans may be due to race differences and environmental conditions.

In conclusion, we found higher and significant positive correlation of SAT resistin mRNA expression with serum resistin, BMI and insulin resistance (HOMA index), suggesting its potential role in development of insulin resistance and thus associated with obesity-related disorders. The findings of this study may have clinical implications but may be validated further on varied populations with large sample sizes.

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COMMENTS

Background

The incidence of obesity has dramatically increased in recent years. Consequently, disturbances in secretion of resistin caused by obesity have an influence on the development of metabolic complications. It regulates insulin sensitivity but the role of resistin in insulin sensitivity is not yet determined. Many studies have reported that resistin decreases insulin sensitivity in rat models but it is unclear in humans. The aim of the present study was to investigate the relationship of subcutaneous adipose tissue (SAT) resistin mRNA expression with body mass index (BMI), homeostasis model assessment (HOMA) and serum resistin in obese postmenopausal Indian women.

Research frontiers

Adipose tissue produces resistin which may play an influential role in energy homeostasis, triglyceride storage and mobilization of fat with increased adiposity, specifically central adiposity. Furthermore, it seems apparent that the pathogenesis of type 2 diabetes mellitus is mediated through the concurrent progression of insulin resistance and subclinical inflammation. The molecular mechanisms for this are less understood. The research hotspot is to establish the relevance of resistin to human diabetes, particularly its effects on the central nervous system and β-cell function.

Innovations and breakthroughs

Previous reports suggested that resistin secreted by visceral adipose tissue is responsible for development of obesity-related problems but we cannot ignore the role of subcutaneous adipose tissue. Most studies have been done in cultured cells but lack fresh adipose tissue. Furthermore, the literature regarding SAT resistin mRNA expression in Asians, especially Indians, is lacking. Our results showed a direct association of SAT resistin mRNA expression with BMI, HOMA and serum resistin levels in postmenopausal obese women.

Applications

The study suggests that resistin secreted by adipose tissue may be responsible for insulin resistance. Selective manipulation of adipocyte hormones offers a dimension to treat insulin resistance.

Terminology

Resistin is a member of a class of cysteine-rich proteins collectively termed resistin-like molecules. Subcutaneous adipose tissue: Most of the remaining non visceral fat is found just below the skin in a region called the hypodermis.

Peer review

The paper investigates SAT resistin mRNA expression in postmenopausal Indian women and its association with insulin resistance. It is well and clearly written.

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Events Calendar 2012

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ICADIT 2012: International conference on Advances in Diabetes and Insulin Therapy
Zurich, Switzerland

January 29-February 3, 2012
Genetic and Molecular Basis of Obesity and Body Weight Regulation
Santa Fe, NM, United States

February 3, 2012
The Future of Obesity Treatment
London, United Kingdom

February 8-11, 2012
5th International Conference on Advanced Technologies and Treatments for Diabetes
Barcelona, Spain

February 9-10, 2012
EC Conference on Diabetes and Obesity Research - Save the Date
Brussels, Belgium

February 21, 2012
Association of Children's Diabetes Clinicians 6th Annual Meeting
Coventry, United Kingdom

February 23, 2012
Diabetes and kidney disease: advances and controversies
Birmingham, United Kingdom

March 1-3, 2012
International conference on Nutrition and Growth
Paris, France

March 7-9, 2012
Diabetes UK Annual Professional Conference 2012
Glasgow, United Kingdom

March 15 -16, 2012
Monogenic Disorders of Insulin Secretion: Congenital Hyperinsulinism and Neonatal Diabetes
Philadelphia, PA, United States

March 15 -17, 2012
2012 DF Con - Diabetic Foot Global Conference
Hollywood, CA, United States

March 19-22, 2012
Society for Endocrinology BES 2012
Harrogate, United Kingdom

March 22-25, 2012
2nd Latin America Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension
Rio de Janeiro, Brazil

March 29-31, 2012
The 4th International Conference on Advances in Diabetes and Insulin Therapy
Riga, Latvia

March 29-April 1, 2012
New Frontiers in Diabetes Management
Ocho Rios, Jamaica

April 2-6, 2012
6th Annual Primary Care Spring Conference: Session 1
Palm Coast, FL, United States

April 4-7, 2012
39th Panhellenic Congress of Endocrinology and Metabolism
Athens, Greece

April 11-13, 2012
ICDM 2012: International Conference on Diabetes and Metabolism
Venice, Italy

April 11-13, 2012
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Venice, Italy

April 16-17, 2012
Paediatric and Adolescent Diabetes
Birmingham, United Kingdom

April 22-25, 2012
9th International Podocyte Conference
Miami, FL, United States

May 9-12, 2012
19th European Congress on Obesity
Lyon, France

May 23-27, 2012
AACE 21st Annual Scientific and Clinical Congress - American Association of Clinical Endocrinologists
Philadelphia, PA, United States

May 24-27, 2012
27th Annual Clinical Conference on Diabetes
Bonita Springs, FL, United States

June 8-12, 2012
American Diabetes Association's 72nd Scientific Sessions
Philadelphia, PA, United States

June 29-August 2, 2012
ESE Summer School on Endocrinology
Bregenz, Austria

August 1-4, 2012
AADE 39th Annual Meeting - American Association of Diabetes Educators
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September 13-16, 2012
EMBO-EMBL Symposium: Diabetes and Obesity
Heidelberg, Germany

October 1-5, 2012
48th European Association for the Study of Diabetes Annual Meeting
Berlin, Germany

November 7-9, 2012
40th Meeting of the British Society for Paediatric Endocrinology and Diabetes
Leeds, United Kingdom

November 8-11, 2012
The 4th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension
Barcelona, Spain

December 4-6, 2012
1st American Diabetes Association Middle East Congress
Dubai, United Arab Emirates

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INSTRUCTIONS TO AUTHORS

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The columns in the issues of *WJD* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Article: To report innovative and original findings in diabetes; (9) Brief Article: To briefly report the novel and innovative findings in diabetes research; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJD*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of diabetes mellitus; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on basic research and clinical practice in diabetes mellitus.

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In the interests of transparency and to help reviewersassess any potential bias, *WJD* requires authors of all papers to declare any competing commercial, personal, political, intellectual, or religious interests in relation to the submitted work. Referees are also asked to indicate any potential conflict they might have reviewing a particular paper. Before submitting, authors are suggested to read "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest" from International Committee of Medical Journal Editors (ICMJE), which is available at: http://www.icmje.org/ethical_4conflicts.html.

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 200201 03498. 2002 Aug 1

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