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Assessing The Utility Of SPISE (Single Point Insulin Sensitivity Estimator) As A Low-Cost Surrogate Marker In Measurement Of Insulin Sensitivity Among CKD Patients.

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ABSTRACT

The increasing evidence of cardiovascular mortality in chronic kidney disease patients requires identification of non-traditional risk factors. Increased insulin resistance has been identified as one such risk factor. However, there are no validated and feasible methods for estimating insulin sensitivity in large-population. Hence this study intends to study insulin sensitivity in non-diabetic CKD patients and correlate with the insulin resistance calculated using HOMA-IR. A comparative study done among CKD patients and control group in a tertiary care hospital in Tumkur. 45 CKD cases and 45 controls were included in the study. Demographic data was collected and Blood samples were collected to assess Fasting blood sugar, fasting insulin levels and lipid profile. Insulin resistance was calculated using HOMA-IR and insulin sensitivity calculated using SPISE formula. Mean age of participants in cases and control group was comparable with 36.11±9.5 years among cases and 35.02±8.7 years among control group. There was a negative correlation between SPISE and HOMA IR indicating inverse relationship between resistance and sensitivity. ROC curve between true-positive rate and false-positive rate showed AUC for SPISE index to be 0.73 ($P < 0.05$, CI: 0.69–0.78). This study indicates that SPISE is useful in assessing insulin sensitivity with the advantage of being easily available in clinical practice, using fasting blood cholesterol and BMI, and without the necessity to analyze insulin levels.

Keywords: CKD, Insulin resistance, HOMA IR, SPISE, cardiovascular mortality, Insulin sensitivity.

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INTRODUCTION

Chronic kidney disease (CKD) is emerging to be an important chronic disease globally [1] affecting poor, vulnerable and marginalised population disproportionately. According to the Global Burden of Disease (GBD) study, approximately 700 million people are affected worldwide, with its prevalence being increased by 33% between 1990 and 2017 [2]. Crucially, the greatest growth in the burden of CKD (prevalence and mortality) is concentrated in low-income communities (LICs), with almost one-third of all patients with CKD living in India and China [2]. Currently, CKD is the third fastest-growing cause of death globally and the only Non-Communicable Disease (NCD) to exhibit a continued rise in age-adjusted mortality [3]. By 2040, CKD is projected to be the 5th highest cause of years of life lost (YLL) globally [4].

CKD is a progressive systemic disorder which contributes to the development and progression of other major NCDs, most notably cardiovascular disease [5]. Approximately 1 in 3 people with diabetes and 1 in 5 with hypertension in High Income Communities (HICs) are affected with CKD, suggesting that the growing disease burden of CKD can be alleviated by controlling diabetes and cardiovascular disease [6].

The increased incidence of cardiovascular mortality in patients with CKD are not completely explained by traditional risk factors such as hypertension, smoking, hyperlipidemia, obesity, diabetes mellitus, or family history of coronary artery disease and hence demands thorough research in identifying the risk factors.

Insulin resistance (IR) is increasingly recognized as a `nontraditional' risk factor and has been associated with increased risk of cardiovascular events and mortality in multiple large community-based cohort studies [7-11]. IR contributes to cardiovascular disease through endothelial dysfunction, oxidative stress, dyslipidemia, systemic inflammation, and activation of the renin–angiotensin– aldosterone system [12]. Insulin resistance is common in end-stage renal disease (ESRD), and possibly also in moderate-to-severe stages of CKD. Therefore, insulin resistance may be an important therapeutic target for reduction of cardiovascular mortality in patients with CKD.

The gold standard method in estimating IR accurately is the euglycemic insulin clamp technique. But this approach is time-consuming, costly, and considered inappropriate for larger-scale or epidemiological research. It has been suggested that other fasting measures, such as the homeostasis model assessment (HOMA-IR) index, the log HOMA-IR index, the quantitative insulin sensitivity check index (QUICKI) and the revised QUICKI index are more clinically appropriate and practical surrogate indices of insulin resistance [13].

However, indices of insulin sensitivity are also available using 0-h and 2-h glucose and insulin values during the standard 75-g oral glucose tolerance test (OGTT), like the Cederholm index [14] and the Matsuda index [15]. Furthermore, a new fasting insulin sensitivity index, SPISE (single-point insulin sensitivity index), has recently been introduced by the RISC and Beta-JUDO investigators as an easily applicable tool in clinical practice, based on the ratio of triglycerides to high-density lipoprotein-cholesterol (TG/HDL) and body mass index (BMI). After several repeated regression models, the best formula for SPISE was presented as:

$$SPISE = 600 \times HDL\text{-}C\ (0.185) / (TG\ (0.2) \times BMI\ (1.338))$$ [16].

Hence, this study is intended to assess the effectiveness of a new index, SPISE (Single point insulin sensitivity estimator) in IR estimation in correlation with HOMA-IR in CKD patients.

METHODOLOGY

The study was conducted in a tertiary care hospital after obtaining ethical clearance certificate from the Institutional Ethics Committee. An informed consent was taken before the collection of the sample. A total of 90 participants were included in the study based on convenient sampling. The study population was selected based on the following inclusion criteria: 45 clinically diagnosed cases of CKD between the age group of 25-50 years were included as cases and 45 healthy individuals who visit the hospital for routine health check-up and willing to be a part of this study were included as control group. Patients with known case of cardiovascular diseases, diabetes mellitus, CKD on dialysis (stage V CKD), those who are on anti-inflammatory drugs, ACE inhibitors, Angiotensin receptor blockers or on diuretics, were excluded.

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A detailed history, including drug history, weight, height, blood pressure was recorded. Body mass index (BMI) was calculated. Around 5ml of blood sample was collected in vacutainers after an overnight fast of 10-12 hours and were subjected to the following analyses: Fasting blood sugar (FBS), fasting insulin levels and lipid profile. Insulin resistance was calculated with following formula:

$$IR_{HOMA} = (I_0 \times G_0)/ 22.5 \text{ (mathematically: } e^{-lnx} = 1 / x)$$

and

Insulin Sensitivity Index SPISE: SPISE = 600 × HDL-C (0.185)/ (TG (0.2) × BMI (1.338))

HOMA IR value of 1.9 and above was considered for insulin resistance. Statistical analyses were performed on Microsoft Excel and SPSS software (version 26.0). The distribution of continuous variables was described as mean ± Standard Deviation and compared using Student t-test. The level of statistical significance was established at $p< 0.05$.

The values of SPISE were correlated with HOMA IR using Pearson correlation coefficient. The sensitivity and specificity for SPISE IR by the estimated formulae was calculated. Receiver operating characteristics curve (ROC) and Area under curve (AUC) was used to evaluate the ability of the formulae to discriminate diseased cases from normal subjects.

RESULTS

A comparative study to evaluate the Insulin resistance among CKD cases and controls done. Mean age of participants in cases and control group was 36.11±9.5 years and 35.02±8.7 years respectively and BMI among cases was 24.02±3.61 and among controls was 24.06 ± 2.84. Both the characteristics were found to be comparable ($p>0.05$) (Table 1).

Table 1: Comparison of demographics and laboratory characteristics of study participants.

Characteristics	Cases		Control		*P value
	Mean	SD	Mean	SD	
Age	36.11	9.535	35.02	8.796	0.65
Total cholesterol	166.91	54.937	171.91	36.427	0.006
Triglycerides	139.22	49.186	143.48	64.303	0.02
HDL	42.38	7.685	47.25	12.704	0.07
LDL	96.68	45.86	110.70	37.319	0.09
VLDL	25.05	14.5	25.25	17.5	0.08
TC: HDL	3.91	1.06	3.77	0.93	0.22
Insulin	18.04	4.07	3.62	1.12	0.0001
BMI	24.02	3.61	24.06	2.84	0.07
FBS	93.93	17.941	90.89	10.384	0.001
HOMA IR	4.1	0.8	0.8	0.2	<0.0001
SPISE	6.6	1.02	6.7	1.4	0.039

*Independent T test

In the current study mean values of total cholesterol among cases was 166 ± 54.9 and among control group was 171.9 ± 36.42. Difference observed between the group was statistically significant with p-value of 0.006. Other variables on cholesterol variations are given in table 1. Mean values of Insulin was more among cases was 18.04± 4.07 as compared to control group (3.62±1.12). Difference observed was statistically found significant with p value of 0.0001. The difference in HOMA-IR values among cases and controls was found to be statistically significant with $p<0.001$.

Mean values of SPISE among cases was 6.6 ± 1.02. and control group was 6.7 ± 1.4, the difference observed among groups was found to be statistically significant by independent T test with p value of <0.05.

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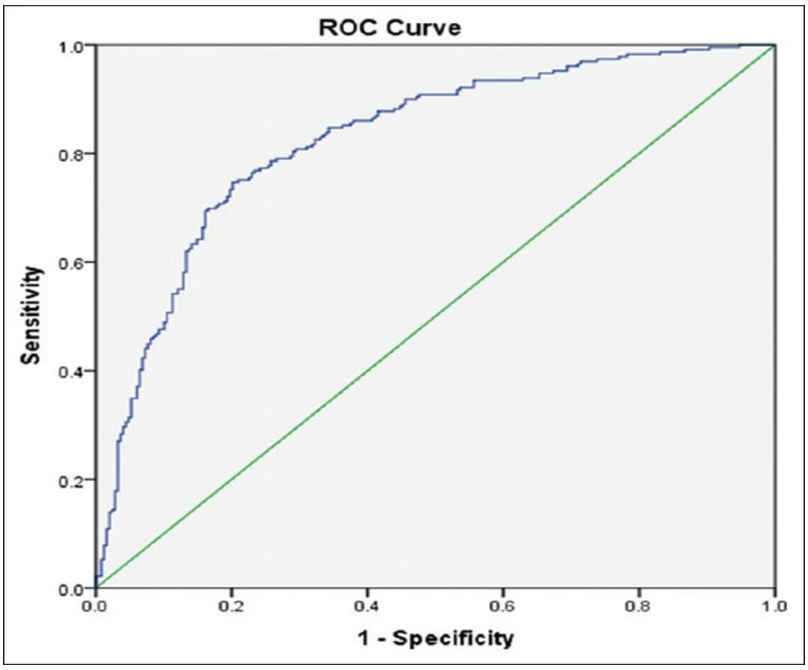
After applying Pearson correlation between HOMA-IR and SPISE among CKD cases, a negative correlation is being observed between both the parameters which signifies the inverse relationship between Insulin resistance as calculated by HOMA-IR and insulin sensitivity as calculated by SPISE. (Table 2).

Table 2: Table showing Pearson correlation between HOMA IR and SPISE in CKD cases.

	SPISE CASES	HOMA-IR CASES
Pearson Correlation	1	-0.035
Sig. (2-tailed)		0.748
N	90	90

ROC curve between true-positive rate and false-positive rate showed AUC for SPISE index to be 0.73 ($P < 0.05$, CI: 0.69–0.78) (Figure 1).

Figure 1: ROC curve for SPISE.



By studying coordinates of ROC, the cut off value of SPISE index for predicting insulin sensitivity among CKD was found out to be 5.92, with sensitivity and specificity of 75% and 80%, respectively.

DISCUSSION

The present comparative cross-sectional study shows insulin sensitivity in CKD calculated using SPISE formula is comparable with HOMA-IR index and has sensitivity and specificity of 75% and 80%, respectively in predicting insulin resistance among CKD cases.

For every given blood concentration of insulin, insulin resistance is commonly described as diminished biologic activity of insulin at its target organs (e.g., liver, skeletal muscles). Clinically, it manifests as dyslipidemia, hyperglycemia, hyperinsulinemia, and glucose intolerance. The etiology of tissue insensitivity to insulin in CKD is multifactorial in nature and depends on classical risk factors peculiar to CKD such as inflammation and oxidative stress, adipokine derangements, vitamin D deficiency, metabolic acidosis, anaemia, and microbial toxins.

Kidney plays a significant role in maintaining glucose homeostasis. Renal glucose production and utilization have been shown in turnover studies employing radio-labelled glucose to be significant aspects of human glucose metabolism [17]. Therefore, it is postulated that renal failure would result in intricate disruptions in the blood glucose presentation, ultimately leading to insulin resistance. Metabolic studies in

people with type 2 diabetes mellitus have shown that insulin does not decrease renal gluconeogenesis to the same degree as it does in hepatic gluconeogenesis in healthy individuals [18]. This finding suggests that insulin resistance exists at the level of kidney glucose metabolism. Studies done by DeFronzo et al [19] and Friedman et al [20] documented normal glucose uptake in the liver and normal hepatic glucose production in chronic kidney failure patients but defective glucose uptake in the skeletal muscle.

Many experimental results have been reported about the involvement of several inflammatory pathways in the development of insulin resistance, which is assumed to be mediated by proinflammatory cytokines and adipokines. Specifically, among CKD patients, the adipokine adiponectin showed promise as a substantial inverse predictor of both fatal and nonfatal cardiovascular events [21].

A study by Shinohara et al. has rekindled interest in insulin resistance in an effort to demonstrate its therapeutic value. The study's findings indicate that, in nondiabetic patients with end-stage CKD, insulin resistance as measured by HOMA-IR is an independent predictor of cardiovascular mortality [22].

The relationship between insulin resistance and cardiovascular mortality in early chronic kidney disease (CKD) is less thoroughly explored, despite mounting evidence of such a correlation in advanced kidney failure.

The present comparative study, including 90 participants with 45 CKD participants and 45 control group collected data on fasting blood variables and HOMA IR report, showed cross-sectionally that the newly introduced fasting insulin sensitivity index SPISE had a similar degree of pearson negative correlation with the HOMA IR test report.

There are connections between the insulin index at hyperinsulinemic euglycemic clamp tests and a number of fasting or OGTT-based insulin resistance indices, according to a 2014 meta-analysis based on 120 publications [23]. The scientists discovered that the fasting surrogate indices that exhibited the strongest correlation coefficients were Rev QUICKI-IR (r¼0.68), QUICKI-IR (r¼0.61), and Log HOMA-IR (r¼0.60). Based on their findings, they recommended that these three be used in large-scale clinical research.

In a study done by Cederholm J et al [24] Area under curve at ROC analysis was 0.80 for SPISE-IR whereas AUC in our present study was 0.73. An even stronger correlation—a Spearman coefficient of 0.69 was found in a recent Japanese study with 111 healthy, non-diabetic men in the 30- to 50-year-old age range [25].

CONCLUSION

Insulin resistance prevails in CKD patients and contributes to the progression of renal disease and a high cardiovascular risk of this condition. This study indicates that SPISE is useful in assessing insulin sensitivity, with the advantage of being easily available in clinical practice using inexpensive tools like fasting blood cholesterol and BMI, and without the necessity to analyse insulin levels. Longitudinal study can be taken up to assess insulin resistance and outcome.

Strength of this study is that we have taken control group similar to cases and limitation is that it's a cross-sectional study.

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