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Evaluation of the circulatory levels of resistin in coronary artery disease with associated co-morbidities

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Abstract--Inflammation is known to be the root cause of the development of coronary artery disease (CAD). Subclinical inflammation is one of the key players in pathophysiology of CAD. An

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inflammatory response leads to the secretion of various adipokines and cytokines. There are various pro-inflammatory markers which could be used to determine the onset of disease, and one such marker is resistin adipokine. The present study evaluates and compares the circulatory concentration of resistin in CAD patients and controls for the determination of its association with CAD. In this study, 58 CAD patients were enrolled and were further subdivided into four groups as per the associated co-morbidities. Various anthropometric and biochemical parameters were assessed. The circulatory levels of resistin were found to be significantly elevated in CAD patients and their subgroups as compared to controls. We conclude that elevated resistin levels in CAD patients suggest a key role of resistin in the development of CAD. The present study also observed that co-morbidities like type 2 diabetes can act as one of the major factors for the elevated concentration of resistin in the circulation of CAD patients with diabetes.

Keywords---Inflammation, Type, Diabetes;Cardiovascular disease, Resistin, Obesity.

Introduction

Cardiovascular diseases are the leading cause of mortality in a developing country like India. Obesity, diabetes, hypertension, and other lifestyle disorders are known to be primary factors instigating cardiovascular disease. Unhealthy diet, obesity, sedentary lifestyle, excessive consumption of alcohol and tobacco are the causal factors responsible for the early development of these metabolic syndromes (Sreenivas Kumar & Sinha, 2020). By far, cardiovascular diseases (CVDs) are the largest cause of death worldwide. In 2015, an estimated 17.9 million deaths were attributed to CVDs. Ischemic heart disease (IHD) and stroke were the two primary causes of CVD-related health loss in all regions of the world (Roth et al., 2017; Ruan et al., 2018). More than 22.2 million individuals would die yearly from CVDs by 2030. Populations in low and middle income countries (LMICs) now account for 75% of CVD deaths, resulting in a 7% decrease in gross domestic product (GDP) in these nations (World Health Organization, 2014). To lower the CVD burden, numerous community-wide initiatives should be implemented with the goal of encouraging population-wide transitions toward healthy behaviour, as well as early disease detection and management (Leon & Maddox, 2015; Mc Namara, Alzubaidi, & Jackson, 2019). Coronary artery disease (CAD) pathophysiology amongst CVD has been extensively investigated by numerous scientific research organizations, but new investigations continue to uncover several additional elements and the participation of multiple biomolecules in the onset and progression of CAD. Subclinical inflammation has been linked to disease commencement and development in the majority of investigations (Libby & Theroux, 2005). Obesity is linked to numerous inflammatory alterations associated with CAD via adipokines released by adipose tissue where further these bioactive chemicals adipokines plays a significant role in atherogenesis (Ouchi, Parker, Lugus, & Walsh, 2011).

Resistin is an adipokine that is hypothesized to be related to inflammatory alterations in CAD (Sinan et al., 2017) with a detrimental influence on the arterial wall, including the stimulation of endothelial cell dysfunction, smooth muscle cell migration and proliferation, and monocyte and macrophage transformation. Resistin is a cysteine-rich peptide hormone that is released primarily from the stromal vascular component of adipose tissue cell that includes peripheral blood mononuclear cells (PBMC), macrophages, and bone marrow cells (Pang & Le, 2006). The expression and secretion of circulating resistin by human mononuclear cells is predominantly in response to inflammatory stimuli, leading to increased circulating levels of resistin (Kunnari, Savolainen, Ukkola, Kesäniemi, & Jokela, 2009; Lu, Shieh, Chen, Hsu, & Chen, 2002; Reilly & Rader, 2003). It is well established that inflammation plays a significant role in the pathogenesis of type 2 diabetes, cardiovascular disease, and obesity (Libby, Ridker, & Hansson, 2009). Previous reported literature have suggested significant role and a direct correlation of elevated serum resistin levels and clinical atherosclerotic progression of cardiovascular disease (Emamalipour, Seidi, Jahanban-Esfahlan, & Jahanban-Esfahlan, 2019; Jamaluddin, Weakley, Yao, & Chen, 2012; Rashid, 2013; Schwartz & Lazar, 2011). On the other hand, other report indicates that resistin is not a potential biomarker and has no clinical association with CAD (Montazerifar, Bolouri, Paghalea, Mahani, & Karajibani, 2016). Thus, in order to have clarity between these contradictory reports, the present study aimed to evaluate and compare the circulatory concentration of resistin in CAD patients and healthy controls for the purpose of determining its association with CAD and other co-morbidities in the Navi Mumbai population.

Materials and Methods

Study design

This comparative randomized study was undertaken at D.Y. Patil Hospital and Research Centre, Navi Mumbai from September 2019 to February 2020. Prior to the patient's enrollment in the study, an approval was obtained from the Institutional Ethics Committee, D.Y. Patil Hospital and Research Centre (Ref no: DYP/IECBH/2019/08). A well-informed written consent was obtained from each of the participants. A total of 58 patients constituting both male and females were enrolled from the Cardiology and CVTS Departments. The study population was selected on the basis of pre-decided inclusion and exclusion criteria. The CAD group was further sub-divided based on presence of co-morbidities like type 2 diabetes mellitus (DM) and hypertension (HTN) as follows,

Group 1-Subjects clinically proven to be CAD patients with DM as co-morbidity,

Group 2-Subjects clinically proven to be CAD patients with HTN as co-morbidity,

Group 3-Subjects clinically proven to be CAD patients with DM and HTN both as co-morbidities and

Group 4- Subjects clinically proven to be CAD patients without DM and HTN as co-morbidities.

Body fat analysis and anthropometric measurements:

Selected subjects were considered for anthropometric assessments. Participant's diet history and exposure to metabolic syndromes (HTN/DM/obesity) were recorded. The body fat analysis was carried out with help of portable digital body fat analyzer and a measuring tape. The waist circumference/hip circumference and height were measured with the help of measuring tape in centimeters. All the parameters were analyzed with the help of the Actofit Smartscale Pro-Max, India and the details were obtained in the form of table within the application software to which it was connected.

Biochemical analysis:

Blood sample from the subjects were collected after 12 h of fasting. The serum was separated and stored in aliquots at -20°C till further analysis. All the routine biochemical investigations like by lipid profile, blood sugar and glycosylated hemoglobin were measured in clinical laboratory of D.Y. Patil Hospital and Research Centre.

Resistin ELISA:

Resistin levels were determined by ELISA technique by using commercially available kits from Krishgen Biosystems.

Statistical analysis:

All data were expressed as mean \pm SD. The data was presented as descriptive statistics. Gender distribution among the CAD subgroups was analyzed using their frequencies. The comparison between CAD patients and controls were performed using independent student's t test. One-way analysis of variance (ANOVA) was used for the comparison of subgroups of CAD. Probability values $<$ 0.05 were considered to be statistically significant. All analysis was performed using IBM SPSS statistical software, version 23.

Results and Discussions

In our study, the patients were divided into the groups on basis of history of comorbidities like DM and HTN. Table 1 represents the distribution of the subjects on basis of gender. A total of 24 subjects were reported to have DM as co-morbidity whereas 14 people revealed history of HTN. Furthermore, 11 people reported both the co-morbidities and 9 subjects confirmed no associated co-morbidities. 79.2% of male versus 20.8% female was found with CAD and DM. The present data indicates that males are more vulnerable to the disease but needs a confirmation considering a larger population. A similar trend was seen in group 2 where 85.7% patients were male and 14.3% were female. Group 3 and group 4 also showed higher percentage of males with CAD in presences and absence of co-morbidities.

Table 1
Gender distribution in the subjects

| Group | Male N (%) | Female N (%) | Total |
|---|-----------------------|-------------------------|--------------|
| Group 1 CAD with DM | 19 (79.2) | 05 (20.8) | 24 |
| Group 2 CAD with HTN | 12 (85.7) | 02 (14.3) | 14 |
| Group 3 CAD with DM and HTN | 09 (81.8) | 02 (18.2) | 11 |
| Group 4 CAD without DM and HTN | 08 (88.9) | 01 (11.1) | 09 |

From worldwide prospective epidemiological research, the development of risk variables and their correlation with the manifestation of various disease have been determined (Bhori, Rastogi, Tungare, & Marar, 2022). Such studies have demonstrated a consistent link between attributes studied in healthy individuals and the prevalence of CAD. Association of age with the disease prevalence has been always of prime importance. Our study reflects increase of CAD incidence with increase in age. The mean age was found to be 40.2 ± 11 in control versus 58.2 ± 9.46 years (Table 2). This difference in age of both the group was found to be statistically significant ($p < 0.001$). This is in agreement to previously published literature that mentions the risk of developing CAD increases with age, and includes age more than 45 years in men and more than 55 years in women (Hajar, 2017). When age of the CAD patients was compared amongst the sub-group made on the basis of co-morbidities the date remained non-significant (Table 3). A low body mass index (BMI) is associated with an increased risk of CAD in its early stages (Alkhawam et al., 2016). However, in the present study no statistical difference was found in the mean BMI values of control and cases (Table 2) as well as amongst the sub-groups (Table 3). Being overweight or obese is considered as a risk factor for cardiovascular disease and metabolic syndrome. As a result, clinicians have been baffled by the wide range of variables involved, because not all the overweight people acquire CAD. Many studies have linked anomalies in the metabolism associated with DM, CAD, and atherosclerosis to an individual's fat distribution, specifically the accumulation of intra-abdominal fat (Singh et al., 2013). CAD patients in our group had significantly ($p = 0.026$) different mean subcutaneous fat percent *i.e.*, $28.55 \pm 7.59\%$ when compared to control ($25.57 \pm 6.60\%$) albeit body and visceral fat percent were comparable in both the groups and comparison remained non-significant (Table 2). Additionally, comparison of sub-groups yielded non-significant outcome for body fat, subcutaneous fat and visceral fat percent (Table 3). On the contrary to our findings, other reports suggests visceral fat to be a better indicator of cardiovascular risk factors (Singh et al., 2013). Furthermore, researchers have reported the increased risk of coronary heart disease associated with obesity may be attributed to the poor metabolic profile associated with increased visceral fat deposition, as opposed to subcutaneous fat, which accounts for more than 85% of total body fat (Canoy et al., 2007). Therefore, the abdominal visceral/subcutaneous adipose tissue ratio can serve as an independent predictor

of mortality and coronary events, independent of cardiovascular risk variables (Ladeiras-Lopes et al., 2017).

A higher incidence and risk of developing CAD have been associated to DM. Impaired fasting blood sugar and glycated hemoglobin (HbA1c) have been used since long time to detect DM (Bhori et al. 2022; Park et al. 2013; Ul-Haque et al. 2019). However, it is well accepted that the HbA1c (glycated hemoglobin) is a better indicator of the severity of diabetes than fasting glucose levels. As a measure of long-term glycemic state, HbA1c values are more advantageous since they provide an average glucose concentration in plasma for two to three months (Hong et al., 2014). In the present study, a significant difference was recorded while comparing mean fasting sugar level ($p<0.001$) and HbA1c ($p<0.001$) in control versus CAD patients (Table 2). Hyperglycemia tends to expedite atherogenesis, apparently by accelerating the synthesis of glycated proteins and advanced glycation end products and/or by exacerbating endothelial dysfunction. These direct effects of hyperglycemia contribute likely to the microvascular and macrovascular disease (Saha, Kuila, & Sharma, 2022). Our report corroborates with the previous literature supporting relation between fasting sugar level and HbA1c with CAD cases (Ewid et al., 2019; Nielson, Lange, & Hadjokas, 2006; Park et al., 2013; Saha et al., 2022). Fasting sugar level and HbA1c was also found to be significantly associated to CAD subgroups when compared amongst themselves and reflects their superior potential to behave as a disease indicator (Table 3).

Hyperlipidemia remains the greatest risk factor for CAD (Haddad et al., 2002). Numerous studies have proven the importance of lipid profile in the pathogenesis of cardiovascular disease (Zhao, Wang, & Qin, 2021). We measured cholesterol, triglyceride, high density lipoprotein (HDL), low density lipoprotein (LDL) and very low-density lipoprotein (VLDL) in all the case and control subjects. When control patients were compared to CAD patients, a significant ($p<0.001$) rise in mean cholesterol, triglyceride, LDL and VLDL was recorded HDL was found to be significantly ($p<0.001$) reduced in CAD patients (Table 2). A significant difference was also noted in cholesterol and LDL for CAD sub-groups when compared amongst themselves (Table 3). Constriction and abstraction of heart arteries, which are strongly linked to the cardiovascular events (CVD), may be affected by elevated triglyceride and total cholesterol levels. Arteriosclerosis may also be induced by an increase in LDL levels, which could lead to atherogenesis. However, those with higher levels of HDL may have a lower risk of cardiovascular disease. As a result, people with high HDL levels may be less likely to develop cardiovascular disease (Zhao et al., 2021). Our results resonate with similar investigation conducted in various populations (Baloch, Devrajani, Baloch, & Pir, 2014; Haddad et al., 2002).

Table 2
Mean anthropometric and biochemical parameters profile of CAD patients in comparison to control.

| Parameter | Control (n=60) | CAD (n=58) | p-value |
|------------------|-----------------------|-------------------|----------------|
| Age | 40.22 ± 11.21 | 58.22 ± 9.46 | 0.001 |

| | | | |
|------------------------------|----------------|----------------|-------|
| BMI | 25.56 ± 5.00 | 24.60 ± 4.60 | 0.288 |
| Body Fat % | 31.40 ± 8.73 | 28.95 ± 8.40 | 0.127 |
| Subcutaneous Fat (%) | 28.55 ± 7.59 | 25.57 ± 6.60 | 0.026 |
| Visceral Fat | 8.15 ± 4.56 | 9.12 ± 4.37 | 0.247 |
| Fasting Sugar (mg/dl) | 93.60 ± 10.06 | 135.49 ± 58.55 | 0.001 |
| HbA1c (%) | 4.74 ± 0.83 | 7.24 ± 2.13 | 0.001 |
| Cholesterol (mg/dl) | 143.54 ± 27.18 | 187.16 ± 37.93 | 0.001 |
| Triglyceride (mg/dl) | 112.05 ± 28.51 | 193.15 ± 81.48 | 0.001 |
| HDL (mg/dl) | 46.74 ± 7.22 | 39.11 ± 6.95 | 0.001 |
| LDL (mg/dl) | 73.53 ± 26.30 | 107.06 ± 35.94 | 0.001 |
| VLDL (mg/dl) | 22.77 ± 5.84 | 40.50 ± 21.28 | 0.001 |
| Resistin (ng/ml) | 2.89 ± 0.42 | 3.61 ± 1.45 | 0.001 |

Resistin adipokine inhibits the action of insulin by interfering with insulin signaling thereby leading to insulin resistance which gives the name to this molecule (Jamaluddin et al., 2012). Resistin is identified to play an important role in augmenting inflammation by stimulation of inflammatory molecules like TNF-Alpha, IL-6 etc. (Fantuzzi, 2005; Ouchi et al., 2011). It also plays a crucial role in stimulating the expressions of NF-Kappa B which further enhances the multiple inflammatory cascades (J. Zhang et al., 2010). Resistin with other inflammatory mediators affects vascular endothelial cells by changing the expressions of cell adhesion molecules and generation of oxidative stress. This process can lead to atherosclerosis and eventually CAD (Verma et al., 2003). Studies on the role of resistin as an independent prognostic biomarker and understanding impact of its imbalance on CAD as well as other disorders is gaining popularity. Thus, we have attempted to evaluate and compare the circulatory concentration of resistin in CAD patients and healthy controls to unfold it's any possible association with CAD. Resistin level was found to 2.89±0.42 in control versus 3.61±1.45 ng/ml in serum of the patients. The mean resistin levels was found to be statistically significant ($p<0.001$) when control group were compared to CAD group (Table 2). This signifies the relationship of increased resistin levels with cardiovascular disease. Also, amongst the CAD subgroups, a significant difference ($p<0.001$) in the mean resistin value was evident (Table 3). An increased resistin levels were recorded in group 1 (CAD+DM) and group 2 (CAD+HTN) as compared to group 4 (CAD+ No co-morbidity). Group 3 (CAD+DM+HTN) showed highest mean resistin level amongst all the subgroups revealing the superior potential of resistin to act as a biomarker in CAD and associated co-morbidities. Resistin is found to stimulate atypical activity of vascular smooth muscle cells in humans. Our results are in line with previously published data that supports the association of resistin with coronary heart disease and DM (Menzaghi et al., 2013; On, Park, Hyon, & Jeon, 2007; Yaturu, Daberry, Rains, & Jain, 2006; J.-Z. Zhang et al., 2017, 2017). Our data contradicts the data published by Montazerifar and colleagues who reported non-significant association of serum resistin level in CAD patients (Montazerifar et al., 2016). In addition to studies demonstrating that resistin levels are elevated in people with stable CAD, there are also studies demonstrating that they are comparable to those of normal populations. In addition, when CRP levels are considered in the analysis, the relationship

between resistin and CAD patients frequently disappears. This indicates that inflammatory parameters and resistin have a close relationship(Yıldırım Ö, 2018).

Table 3: Mean anthropometric and biochemical parameters profile of sub-CAD patient's categories.

| Parameter | Group 1 CAD+DM (n=24) | Group 2 CAD+HTN (n=14) | Group 3 CAD+DM+HTN (n=11) | Group 4 CAD+ No co- morbidity (n=9) | p- value |
|-----------------------|-----------------------------|------------------------------|---------------------------------|---|-------------|
| Age of Patients | 58.66 ± 9.91 | 56.28 ± 9.08 | 59.81 ± 10.11 | 58.11 ± 9.10 | 0.821 |
| BMI | 24.24 ± 4.68 | 25.70 ± 5.67 | 24.42 ± 3.62 | 24.09 ± 4.03 | 0.791 |
| Body fat (%) | 29.65 ± 10.99 | 30.16 ± 4.66 | 28.14 ± 7.15 | 26.19 ± 6.60 | 0.687 |
| Subcutaneous fat (%) | 24.96 ± 7.80 | 27.45 ± 3.94 | 25.71 ± 7.14 | 24.08 ± 6.04 | 0.625 |
| Visceral fat | 8.50 ± 4.50 | 10.92 ± 4.49 | 9.63 ± 3.82 | 7.33 ± 4.03 | 0.212 |
| Fasting sugar | 142.99 ± 36.68 | 100.04 ± 15.04 | 192.90 ± 97.11 | 100.44 ± 10.88 | 0.000 |
| HbA1c | 7.53 ± 1.58 | 5.77 ± 0.89 | 9.53 ± 2.90 | 5.96 ± 0.50 | 0.000 |
| Cholesterol (mg/dl) | 188.79 ± 36.41 | 198.50 ± 35.89 | 192.82 ± 37.46 | 158.22 ± 37.07 | 0.075 |
| Triglycerides (mg/dl) | 198.33 ± 81.04 | 190.57 ± 31.13 | 203.30 ± 131.30 | 170.91 ± 67.16 | 0.821 |
| HDL (mg/dl) | 39.27 ± 7.01 | 40.62 ± 5.70 | 37.88 ± 9.14 | 37.84 ± 6.15 | 0.734 |
| LDL (mg/dl) | 106.48 ± 36.67 | 119.79 ± 36.69 | 109.27 ± 35.18 | 86.14 ± 28.61 | 0.018 |
| VLDL (mg/dl) | 44.15 ± 26.62 | 38.06 ± 6.27 | 40.78 ± 26.06 | 34.19 ± 13.43 | 0.652 |
| Resistin (ng/ml) | 3.07 ± 0.55 | 3.35 ± 0.97 | 5.10 ± 2.49 | 2.99 ± 0.57 | 0.001 |

The clinical, genetic, and epidemiological studies carried out till date have helped strengthen the association between resistin and the prevalence, severity, and outcome of metabolic diseases. Further it would be interesting to determine if blocking of resistin function, using antibody neutralization or use of an antagonistic resistin receptor would support the use of resistin as a viable therapeutic target in humans with diabetes or cardiovascular disease in pre-clinical models such as the humanized mouse.

Limitations: This study is one of the first few studies carried out on circulatory levels of resistin in Indian population and it is a self-funded study. Hence number of cases included in the present study were limited. However, further cohort studies may provide a broader picture when studied on larger population.

Conclusion

The present study reports a higher visceral fat and circulatory levels of resistin in CAD patients than controls. Further, it has been observed that resistin levels

were incriminatingly increased in CAD patients with co-morbidities like type 2 diabetes mellitus and hypertension. An imbalance in the levels of resistin could be a probable cause for the development of early inflammation, metabolic disorders, and CAD.

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