Clinico-Biochemical Correlation Between Psoriasis and Insulin Resistance

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Received: 1 October 2013 / Accepted: 11 December 2013 / Published online: 23 January 2014
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Abstract Psoriasis is a chronic inflammatory disease associated with an increased insulin resistance, obesity and cardiovascular risk. The present study was aimed to assess insulin resistance and pattern of body fat deposition in psoriasis. Body mass index (BMI) and waist circumference (WC) were measured in 40 psoriatic patients and 46 age- and sex-matched control subjects. Fasting blood glucose (FBG) and serum insulin level were measured by standard photometric method and ELISA respectively. HOMA-IR (homeostatic model of insulin resistance) was calculated by appropriate software. The results indicated that case and control groups were comparable in terms of age and sex ($p = 0.934$) with an increased prevalence of psoriasis among male subjects (60 %). FBG and mean WC between the two groups were statistically not significant (p value = 0.271 and 0.21 respectively). BMI was significantly higher in case

group compared to the control group ($p = 0.049$). Serum insulin level and insulin resistance in the psoriatic patients were significantly higher (p value <0.001). Multiple regression analysis revealed that insulin resistance (measured by HOMA) was dependent on BMI and WC at a significance level of $p < 0.001$ and 0.043 respectively. Therefore, the psoriatic patients in this region have significantly high amount of fasting serum insulin level along with an increased IR though their FBG level remains normal. Furthermore, these abnormalities are significantly dependent on total body fat as well as abdominal fat deposits. We suggest that psoriatic patients need to be evaluated for metabolic syndrome and managed accordingly.

Keywords Psoriasis · Insulin resistance · Body mass index · Waist circumference

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Introduction

Psoriasis is a common, chronic, disfiguring, inflammatory and proliferative condition of the skin, in which both genetic and environmental influences have critical roles [1]. It is an immune mediated, multifactorial disease caused by phenotypic diversity and genetic heterogeneity [2]. It affects ~2–3 % of global population [3, 4]. The multifactorial basis of this disease is manifested by many metabolic complications. It is found to be associated with diabetes mellitus, obesity, and dyslipidemia [5–7]. The prevalence of psoriasis was reported to be 9 % in diabetic patients by Romano et al. which is higher than the value of 4 % among normal population. Some recent studies also reported higher prevalence of diabetes mellitus in psoriatic patients. Insulin resistance has been a classical feature in these patients and is associated with several

metabolic and immunological derangements. A well-established pathway linked atherosclerosis to obesity via overproduction of tumour necrosis factor α (TNF- α), which also contributes to insulin resistance and development of type 2 diabetes mellitus [8, 9]. Studies have documented the risk of psoriasis to be directly related to the body mass index (BMI) reflecting a close causal relationship between obesity and psoriasis [8, 10]. Studies conducted by Boehncke et al. [11] on psoriasis patients showed signs of insulin resistance along with definite correlations between BMI and HOMA ($p < 0.02$). Krishnamoorthy and co-workers [12] reported that psoriasis patients had more insulin resistant (HOMA-IR: 3.5 vs. 1.4, $p < 0.001$) and higher waist circumferences (WC) (40 cm vs. 35.5 cm, $p < 0.001$) than their normal counterparts.

Psoriasis and obesity show many shared cytokines that are known to contribute to features of the metabolic syndrome such as hypertension, dyslipidemia and insulin resistance [13]. Each of primary adipokines including IL-6, TNF- α , adiponectin and Plasminogen activator inhibitor type-1 (PAI-1) plays multiple roles in inflammation, metabolism and endothelial cell regulation. Importantly, visceral adiposity is associated with an elevation of TNF- α , IL-6, PAI-1 [14]. However, the relationship between fasting blood glucose (FBG) and psoriasis is not consistent and has been found to vary among different studies. A study on insulin resistance in psoriasis was conducted by Brenelli et al. by measuring oral glucose tolerance test (OGTT) and intravenous insulin tolerance test (15-min ITT). No significant differences in mean plasma glucose levels were detected between psoriatic patients and normal individuals [15]. On the other hand, study by Pereira et al. [16] showed the prevalence of impaired fasting glucose, impaired glucose tolerance, and diabetes mellitus in psoriatics to be 5.2, 9.1, and 32.5 %, respectively, as compared to 6.5, 3.3, and 15.2 % in the control subjects. From these conflicting results we hypothesized that there might be an association of insulin resistance and central obesity with the disease process in the psoriatic patients in our study population. Accordingly, we made an effort to assess the association of these parameters with psoriasis in our region through evaluating FBG, IR, BMI and WC in them.

Materials and Methods

Selection of Cases and Controls

The present hospital based, cross sectional study was undertaken in the Departments of Dermatology & Biochemistry, Burdwan Medical College & Hospital, Burdwan in the period between March 2011 to February 2012. 40

patients suffering from psoriasis (clinically and histopathologically confirmed) attending the dermatology Out Patient Department (OPD) with age >15 years, duration of disease <2 years (to avoid the metabolic complications of immunosuppressive therapy), not receiving any systemic treatment were selected as the case group by the method of convenience. Age and sex-matched 46 healthy persons attending OPD for cosmetic purposes (Melasma, acquired and congenital melanocytic nevus, epidermal nevus, and milia) were included in the study as control subjects. Patients suffering from diseases that cause secondary hyperglycemia such as cushing syndrome, hyperthyroidism, corticosteroid therapy etc. and patients also suffering from nephrotic syndrome, chronic renal failure, liver disease, connective tissue disorder were excluded from study. Obese patients (BMI >30 kg/m²), patients on medications such as beta blockers, thiazides, retinoids, cyclosporine, hypoglycaemic drugs, pregnancy and lactating mothers and patient having history of smoking and alcoholism were also excluded. Written consents were obtained from both case and control subjects before the study. The study strictly adhered to the ethical guidelines of the Helsinki Declaration 1975, revised in 2000 for human studies and ethical clearance was obtained from the properly constituted institutional ethical committee before the start of the study.

Measurement of Study Parameters

Fasting plasma glucose level were measured by standard photometric technique following the glucose oxidase peroxidase (GOD-POD) method [17]. Serum insulin was assayed by ELISA from Accubind (USA). Insulin resistance was calculated by the homoeostatic model assessment (HOMA) from the values of fasting glucose levels and serum insulin. The homoeostatic model assessment (HOMA) estimates steady state beta cell function (%B) and insulin sensitivity (%S), as percentages of a normal reference population. These measures correspond well but are not necessarily equivalent to non-steady state estimates of beta cell function and insulin sensitivity derived from stimulatory models such as the hyperinsulinemic clamp, the hyperglycaemic clamp, the intravenous glucose tolerance test (acute insulin response, minimal model), and the OGTT (0–30 delta I/G). For this calculation we took the help of HOMA calculator. (HOMA Calculator 2.2.2 released in December 2007). This calculator can also be obtained from <http://www.dtu.ox.ac.uk/homa>. As HOMA is a steady state model, only clinically realistic values that would be seen in a fasting subject were used (plasma glucose 63–450 mg/dl and Plasma insulin 2.79–55.76 μ IU/ml). All clinically diagnosed cases of psoriasis were confirmed by histopathology.

Table 1 Independent sample *t* test for different parameters in case and control groups

Parameters	Case (<i>N</i> = 40) mean (SD)	Control (<i>N</i> = 46) mean (SD)	<i>t</i>	<i>p</i> value
FBG (mg/dl)	90.475 (10.205)	93.782 (16.282)	−1.109	0.271
Insulin (μIU/ml)	33.523 (16.12)	8.3 (4.08)	10.247	<0.001*
HOMA-IR	4.14 (1.98)	1.097 (0.577)	9.929	<0.001*
BMI	24.013 (2.572)	22.852 (2.78)	1.999	0.049*
WC (cm)	86.525 (10.043)	84.13 (7.47)	1.264	0.210

* Difference is significant ($p < 0.05$) at confidence interval (CI) of 95 %

Data Analysis

The data obtained were analysed for differences between mean values of the case and control group. Multiple regression analysis was performed for analysing the predictive values of central obesity, general obesity and FBG values on insulin resistance. Statistical analyses were performed with the help of SPSS software version 17.0 for Windows. For all statistical analyses the *p* value was considered to be significant at $p < 0.05$.

Results

In the case group serum insulin level and insulin resistance marker HOMA-IR were found to be significantly raised than those of control group ($p < 0.001$). However, FBG level did not show any significant difference between the case and control groups ($p = 0.271$).

BMI was significantly higher in psoriatic group than in age- and sex-matched control ($p = 0.049$) without any significant increase in the WC parameter indicating a definite increase in overall body weight without any marked change in abdominal obesity ($p = 0.21$).

The multiple regression analysis in Table 2 shows the predictive values of FBG, WC and BMI on HOMA-IR when taken together. The results revealed that obesity of both type i.e. general as well as abdominal fat deposition were significant predictors of insulin resistance in the psoriatic patients.

Discussion

In the present study, we found significantly higher degree of insulin resistance along with an increased BMI in the case group. Although we observed an increased WC in the case group, its difference from control subjects was not statistically significant ($p = 0.21$, Table 1). The increasing risks for developing atherosclerosis and cardiovascular diseases in psoriasis are attributed to many metabolic complications like diabetes mellitus, obesity, and dyslipidaemia. The results of our present study signified that these metabolic abnormalities in psoriasis may be confounded through an

increased insulin resistance and overall body fat deposition more than the abdominal fat accumulation. However, the increased insulin resistance in the psoriasis patients in our study group (Table 1) was found to be significantly dependent on overall obesity (BMI) and abdominal adiposity (WC) both as evident from the multiple linear regression study (Table 2) that suggested a cryptic predictive role of central obesity in causation of metabolic sequelae of psoriasis by raising insulin resistance in these patients. Our findings are corroborated by several studies worldwide that have shown raised serum insulin, increased HOMA-IR, and raised BMI in psoriatic patients. Although, abdominal fat deposition did not show any overt increase in the case group, its significant predictive value (beta coefficient: 0.314, $p = 0.043$, Table 2) for development of insulin resistance strengthened its role as potential risk factor in these patients. The association between abdominal fat accumulation and risk of chronic diseases, including type II diabetes and coronary heart disease, has long been recognized. Insulin resistance may be a key factor in this link. Many studies have pointed to an association between insulin resistance and intra-abdominal fat accumulation (visceral obesity). One such potential causal link is the release of non-esterified fatty acids from visceral fat into the portal vein, so that they have direct effects on hepatic metabolism. Visceral fat has been shown in many studies to exhibit a high rate of lipolysis compared with subcutaneous fat depots [18–20]. Furthermore visceral fat pumps out immune system chemicals called cytokines—for example, tumour necrosis factor (TNF) and interleukin-6. The direct secretion of IL-6 into the portal vein has important metabolic consequences because IL-6 stimulates hepatic acute-phase reactant production, impairs insulin-mediated glycogenesis, and stimulates hepatic gluconeogenesis [21]. Psoriasis is associated with inflammatory cytokines [22, 23]. These cytokines might play an important role in increasing insulin resistance in them. For example, TNF may lead to insulin resistance through a variety of pathways such as impairing insulin signalling by inhibiting the tyrosine kinase activity of the insulin receptor; by activating peroxisome proliferator-activated receptor (PPAR) which promotes epidermal proliferation and modulates adipogenesis and glucose metabolism; and by suppressing adiponectin secretion from adipocytes, which is an important anti-inflammatory

Table 2 Multiple linear regression analysis showing the dependence of insulin resistance on different parameters in the case group ($N = 40$)

Model		Unstandardized coefficients		Standardized coefficients	<i>t</i>	Sig.
		B	SE	Beta		
1	(Constant)	−13.679	.446		−30.652	<0.001
	FBG	−.003	.009	−.016	−.292	.772
	BMI	.530	.112	.692	4.726	<0.001
	WC	.062	.030	.315	2.085	.043

Dependent variable HOMA-IR

molecule that also functions in regulating insulin sensitivity [24–26]. This might explain why in spite of increased body fat psoriatic patients become more insulin resistant.

Furthermore, both general obesity and central obesity are well known factor for causing insulin resistance through several mechanisms. Insulin stimulates differentiation of preadipocytes to adipocytes. In adipocytes, insulin promotes lipogenesis by stimulating the uptake of glucose and lipoprotein-derived fatty acids and by inducing ADD-1/SREBP-1c, which regulates genes promoting fatty acid synthesis and lipogenesis, not only in adipocytes but also in hepatocytes. Insulin may also regulate transcription through Forkhead transcription factors. Insulin diminishes triglyceride breakdown by inhibiting lipolysis. Many of these metabolic pathways are regulated by the PI3K signaling pathway [27]. These explain the dependence of insulin resistance to BMI and WC in our study population.

Limitations

The present study has some potential limitations to be mentioned. Severity of psoriasis by the psoriasis area severity index or PASI score could not be determined as most of the patients attended our department after receiving topical treatments. Parameters like some apolipoproteins (Apo B, Apo A-1) and highly selective C-reactive protein (hs-CRP) which are important determinants of atherogenesis and resulting cardiovascular disease could not be included in this study.

Conclusion

Despite these limitations, the study provided important insights into the association of psoriasis and insulin resistance and increased body fat deposition that may herald an impending risk factor for cardiovascular disease in future. It will be therefore prudent to follow-up and monitor psoriasis patients for metabolic syndrome or its sequelae. Our study also suggested that psoriasis is no longer a disease of skin; rather it has far reached implications

involving some other vital organ systems. An appropriate knowledge regarding the biochemical basis of this association will help to develop a better understanding of the disease process and to make substantial modifications in the management and prognosis of psoriasis.

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