Psoriasis and Insulin Resistance

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Abstract

Background: Psoriasis is a chronic and debilitating inflammatory disease associated with serious co-morbidities, with increased prevalence of the metabolic syndrome, in which insulin resistance (IR) is often considered as its central component.

Objective: To detect IR and impaired glucose tolerance (IGT) in psoriatic patients who do not have clinical criteria of metabolic syndrome and their possible relation to the severity of the disease.

Methods: A prospective case-control study included 30 psoriatic patients with different severities and clinical variants, and 30 apparently healthy individuals were chosen as controls.

Results: Our results showed significant increase in the rates of IGT with decline in beta cell function and significant IR in psoriatic patients in comparison to controls with no significant correlation to severity of the disease measured by psoriasis area and severity index (PASI) score. Both fasting serum insulin and IR were higher in female cases with statistically significant difference when compared to males. This suggests that female psoriatic cases may carry high diabetes mellitus (DM) risk.

Conclusion: Psoriatic patients, in the absence of clinical criteria of metabolic syndrome show increased rates of both IR and IGT. Thus psoriasis as a disease entity has an association with IR and may be considered as a hallmark of IR. The detection of IR has an important value in reducing the risk of DM and prevents its complications and other components of insulin resistant syndrome (IRS) in psoriatic patients.

Key Words: Psoriasis – Insulin resistance – Impaired glucose tolerance – Metabolic syndrome.

Introduction

Psoriasis is a common chronic inflammatory skin disease characterized by spontaneous remissions and exacerbations [1]. It affects approximately 0.6–4.8% of the general population [2]. There have been increasing reports that psoriasis may be associated with a high risk of co-morbidities; psychiatric disease, obesity, cancer, autoimmune diseases, cardiovascular and metabolic diseases. It is unclear if these associations are due to the pathophysiology of psoriasis, therapy or psoriasis-associated behaviours (e.g., smoking and alcohol) [3].

Psoriatic patients have an increased prevalence of the core components of metabolic syndrome including; obesity, dyslipidemia, non alcoholic fatty liver disease, insulin resistance (IR) and diabetes mellitus (DM). The relationship between psoriasis and metabolic syndrome is likely linked to the underlying chronic inflammatory nature of psoriasis. The molecular mechanisms involved in psoriasis-associated dysregulation of metabolic function are believed to be due to the action of increased levels of pro-inflammatory factors, such as tumor necrosis factor alpha (TNF-α) [4]. The risk for metabolic syndrome in psoriatic patients increases with the duration, severity of psoriasis as well as with the extent of body involvement [5]. This emphasizes the need for treatment of patients with moderate to severe psoriasis and, in addition, makes it mandatory to more closely pay attention to concomitant diseases particularly the metabolic syndrome [6].

IR presents when an abnormally large amount of insulin (endogenous or exogenous) is required for a normal biologic response [7]. Impaired glucose tolerance (IGT) is a metabolic state intermediate between normal glucose homeostasis and DM [8]. Thus the detection of IR in psoriatic patients could prevent DM and its complications. High prevalence of DM in patients with psoriasis has long been recognized [9]. The association between psoriasis and DM is possibly related to the presence of IR in psoriatic patients [10].
The aim of this work: Was to detect IR and IGT in psoriatic patients who do not have clinical criteria of metabolic syndrome and evaluate their possible relation to the clinical variants, duration and severity of psoriasis.

Subjects and Methods

A prospective case-control study was performed involving 30 psoriatic patients with different clinical variants and severities (group A) and 30 apparently healthy age- and sex-matched individuals as a control group (group B). They were the out-patient department of Dermatology School of Medicine-Cairo University between June-December 2007.

Patient’s inclusion criteria included: Absence of family history of type I or II DM, no obesity; body mass index (BMI) less than 30; no previous intake of any systemic corticosteroids or methotrexate (within the previous six months), and women should not be pregnant, should be studied in the follicular phase (cycle days 3-8) of the menstrual cycle and should not be using any hormonal contraception (for three months).

Each patient underwent: Complete history taking, clinical examination, including assessment of the severity of psoriasis according to (PASI) score and the weight, height of each patient were measured and the BMI was calculated.

Laboratory tests include: Blood glucose levels (Fasting and 2hrs-post-prandial) were performed by using glucose oxidase (colorimetry) and fasting serum insulin level was assessed using ELISA.

Technique of laboratory methods:

Sampling: This was done by taking two samples:

- Fasting samples: 4ml of blood (2ml for fasting blood glucose (FBG) level measurement and 2ml for measuring fasting plasma insulin).

- Two hours postprandial samples: 2ml of blood for blood glucose level measurement (2-h.pp). Serum was separated by centrifugation of the blood samples at 2000xg.

Estimation of serum glucose levels: Both fasting and 2-hours postprandial serum glucose levels were measured using a glucose oxidase technique (colorimetry). To convert blood glucose readings: Divide the mg/dL by 18 to get mmol/L (or multiply by 0.055) then multiply the mmol/L by 18 to get mg/dL (or divide with 0.055). Separated serum for measuring fasting insulin was stored at −80°C until processed.

Estimation of fasting serum Insulin: Serum insulin was measured by Enzyme Immunoassay (ELISA), using DRG Human Insulin EIA-2935. This kit provides a method for the quantitative determination of insulin in human serum.

Evaluation of insulin secretion and insulin sensitivity: The insulin secretion and insulin sensitivity indices were calculated by using the following equations derived from fasting measurements of glucose and insulin:

- Insulin secretion [homeostasis model assessment (HOMA) beta cell index]: HOMA beta cell index was used as beta cell function index. HOMA beta cell index (µU/mmol)= 20x fasting insulin/(fasting glucose 3.5) [11]

- Insulin sensitivity [HOMA-IR index]: HOMA-IR index was used as insulin sensitivity index. HOMA-IR (µU/mmol) = (fasting insulin x fasting glucose)/22.5 [12].

Estimation of IR:

Insulin resistance (IR) was estimated based on cut-off value of fasting serum insulin level ≥13 µU/mL according to Ludwig et al. [13] and/or HOMA-IR ≥3.2 according to Marquis-Vidal et al. [14].

Estimation of impaired glucose tolerance (IGT): Based on fasting and two-hour blood glucose levels impaired glucose tolerance was estimated.

Impaired fasting glucose (IFG) = FBG level: 100-125mg/dL.

Impaired glucose tolerance (IGT2h.pp) = 2-h. PP level: 140-199mg/dL.

These glucose levels are above normal but below the level that is diagnostic for diabetes so, IFG and/or IGT2h.pp were considered as “impaired glucose tolerance (IGT)” or “impaired glucose regulation (IGR)” or “pre-diabetes” group [15].

Statistical methods:

Data were coded and entered using the statistical package SPSS version 12. Data were summarized using mean and standard deviation (SD) for quantitative variables and percent for qualitative variables. Comparisons between groups were done using Chi-Square test for qualitative variables and independent Samples t-test and ANOVA (analysis for variances) for normally distributed quantitative variables. Non parametric Mann-Whitney test and Kruskal-Wallis test were used for abnormally distributed qualitative variables. Correlations were done to test the relation between quantitative variables. p-value less than 0.05 was considered as statistically significant.
Results

The study included 30 patients with psoriasis (group A) (20 males (66.7%) and 10 females (33.3%), with the median age of 48.23 ± 15.7, and age range of 13 to 70). The mean body mass index (BMI) in group A was (24.9 ± 2.5). The duration of illness ranged between 5 months and 35 years with a mean of (9.1 ± 8.2y). The psoriasis area and severity index (PASI) score ranged between 2.4-29.4 with a mean of (10.4 ± 5.7) (Table 1). In addition, 30 healthy volunteers (group B) were chosen as control subjects for comparison of the results (20 males and 10 females, with an age range from 15-65 years). Both patients and controls were sex and age matched. Both fasting and 2-h.pp blood glucose levels were significantly higher in group A than group B with ($p$-value=0.003) (Table 2). There was no significant relation between blood glucose levels and age, sex, BMI of the patients, duration, PASI score or clinical variants of psoriasis.

Fasting serum Insulin levels showed no statistically significant difference between group A and group B ($p$=0.8). Female patients had higher fasting insulin levels than male patients (12.2 ±6.1 Vs. 5.7 ±3.7 respectively) and the difference was statistically significant ($p$=0.003). Fasting insulin levels showed no significant relation with the age, BMI of the patients, duration, PASI score or clinical variants of psoriasis.

The results showed no statistically significant difference in insulin secretion (using HOMA beta cell index) between group A and group B ($p$=0.1). No significant relation between insulin secretion and age, sex, BMI of the patients, duration, PASI score or clinical variants of psoriasis was detected.

There was no statistically significant difference in HOMA-IR index [indicative of insulin sensitivity] between group A and group B ($p$=0.5). Although, among cases, HOMA-IR index was higher in female patients than male (2.7 ±1.3 Vs. 1.3 ±0.8 respectively) with a statistically significant difference ($p$=0.003), which indicated that female patients had higher insulin sensitivity than male patients. HOMA-IR indices showed no significant relation with age, BMI of the patients, duration, PASI score or clinical variants of psoriasis.

As regards IR, we found that five patients (16.7%) had IR (out of whom four had combined elevated insulin and HOMA-IR and one had elevated insulin level only) with statistically significant difference when compared to healthy controls ($p$-value=0.052 border line significant), Fig. (1). These data showed that IR was higher in psoriatic cases than controls.

All IR patients were females with a mean age of (33.6 ±18y) and different clinical variants of psoriasis (two Psoriasis vulgaris, two guttate and one pustular psoriasis). Their mean duration of disease was (3.2 ±1.9y) with a mean PASI score of (11.5±5.6). There was no statistically significant difference regarding the clinical variants, duration and severity of psoriasis, between IR (+ve) and non IR (–ve) cases ($p$-value >0.05). These five female cases with IR had significant increase in the level of HOMA beta cell index compared to non IR cases ($p$=0.008). This result indicates that IR cases have decreased tissue sensitivity to insulin with beta cells hyper secretion and compensatory hyperinsulinaemia.

Based on fasting and two-hour blood glucose levels, ten patients (33.3%) had IGT, Fig. (2), out of which, six patients (20%) had IFG, and seven patients (23.3%) had IGT2h.pp with statistically significant difference ($p$-value=0.024, 0.011 respectively) as compared to normal controls, while, three patients had combined IFG and IGT2h.pp. The ten psoriatic patients who had IGT were eight...
males and two females with a mean age of $(53.7 \pm 10.7y)$ of different clinical variants of psoriasis (five psoriasis vulgaris, two guttate and three pustular). Their mean duration of disease was $(9 \pm 6.5y)$. According to PASI score, six had mild psoriasis, three presented with moderate psoriasis and one with severe psoriasis. Among the cases, there was no statistically significant difference regarding the clinical variants, duration and severity of psoriasis, between IGT (+ve) and non IGT cases (–ve) ($p$-value $>0.05$). In addition, cases with IGT had significant decrease in the level of HOMA beta cell index ($p=0.02$) compared to cases without IGT.

Table (1): Clinical data of psoriatic patients.

<table>
<thead>
<tr>
<th>No</th>
<th>Sex</th>
<th>Age (ys)</th>
<th>BMI</th>
<th>Clinical Variant</th>
<th>Duration (ys)</th>
<th>PASI score</th>
</tr>
</thead>
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<tr>
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<td>65</td>
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<td>P. Vulgaris</td>
<td>4</td>
<td>29.4</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
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<td>25.4</td>
<td>P. Vulgaris</td>
<td>4</td>
<td>4.5</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
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<td>15</td>
<td>16.2</td>
</tr>
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<td>4</td>
<td>8.1</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>58</td>
<td>23.03</td>
<td>P. Vulgaris</td>
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<td>11.5</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>33</td>
<td>22.15</td>
<td>Guttate P.</td>
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<td>5.9</td>
</tr>
<tr>
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<td>42</td>
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<td>22</td>
<td>15.3</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
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</tr>
<tr>
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<td>4.5</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>60</td>
<td>23.3</td>
<td>Guttate P.</td>
<td>15</td>
<td>8.6</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>36</td>
<td>25.02</td>
<td>Pustular P.</td>
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<td>8.5</td>
</tr>
<tr>
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<td>59</td>
<td>27.7</td>
<td>Pustular P.</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
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<td>M</td>
<td>58</td>
<td>25.3</td>
<td>P. Vulgaris</td>
<td>10</td>
<td>16.2</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
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<td>24.4</td>
<td>P. Vulgaris</td>
<td>5</td>
<td>2.8</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>53</td>
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<td>Pustular P.</td>
<td>4</td>
<td>11.6</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>65</td>
<td>27.1</td>
<td>Pustular P.</td>
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<td>3.2</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>27</td>
<td>21.3</td>
<td>P. Vulgaris</td>
<td>0.4 (5 months)</td>
<td>14.1</td>
</tr>
<tr>
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<td>M</td>
<td>69</td>
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<td>P. Vulgaris</td>
<td>15</td>
<td>4.9</td>
</tr>
<tr>
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<td>M</td>
<td>31</td>
<td>28.08</td>
<td>P. Vulgaris</td>
<td>25</td>
<td>12</td>
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<tr>
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<td>39</td>
<td>27.6</td>
<td>P. Vulgaris</td>
<td>5</td>
<td>10.6</td>
</tr>
<tr>
<td>21</td>
<td>M</td>
<td>66</td>
<td>21.4</td>
<td>P. Vulgaris</td>
<td>3</td>
<td>15.2</td>
</tr>
<tr>
<td>22</td>
<td>M</td>
<td>57</td>
<td>26.2</td>
<td>P. Vulgaris</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>23</td>
<td>M</td>
<td>66</td>
<td>23.1</td>
<td>Pustular P.</td>
<td>6</td>
<td>9.2</td>
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<tr>
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<td>47</td>
<td>24.7</td>
<td>P. Vulgaris</td>
<td>4</td>
<td>8.6</td>
</tr>
<tr>
<td>25</td>
<td>F</td>
<td>28</td>
<td>24.6</td>
<td>P. Vulgaris</td>
<td>13</td>
<td>9.8</td>
</tr>
<tr>
<td>26</td>
<td>F</td>
<td>13</td>
<td>23.4</td>
<td>Guttate P.</td>
<td>2</td>
<td>11.2</td>
</tr>
<tr>
<td>27</td>
<td>F</td>
<td>53</td>
<td>24.6</td>
<td>Guttate P.</td>
<td>0.8 (10 months)</td>
<td>16.2</td>
</tr>
<tr>
<td>28</td>
<td>F</td>
<td>15</td>
<td>24.3</td>
<td>Pustular P.</td>
<td>3</td>
<td>16.9</td>
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<tr>
<td>29</td>
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<td>55</td>
<td>26.6</td>
<td>P. Vulgaris</td>
<td>20</td>
<td>4.9</td>
</tr>
<tr>
<td>30</td>
<td>F</td>
<td>30</td>
<td>24.2</td>
<td>P. Vulgaris</td>
<td>10</td>
<td>9.8</td>
</tr>
</tbody>
</table>

Table (2): Blood glucose levels in both cases and controls.

<table>
<thead>
<tr>
<th>FBG (mg/dl)</th>
<th>Cases</th>
<th>SD</th>
<th>2-h. pp (mg/dl)</th>
<th>Cases</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cen</td>
<td>93.1</td>
<td>16.4</td>
<td>0.003</td>
<td>122.9</td>
<td>23.9</td>
</tr>
<tr>
<td>Controls</td>
<td>82.5</td>
<td>9.2</td>
<td></td>
<td>107.2</td>
<td>13.8</td>
</tr>
</tbody>
</table>

Where $p<0.05$ (highly significant difference).

Discussion

While psoriasis causes significant morbidity, it is not generally associated with mortality. However, conditions linked with psoriasis, like metabolic syndrome, are associated with excess mortality [16]. These conditions share etiologic features and health consequences that directly correlate with the severity of the psoriatic disease [8]. Therefore, identification and treatment of modifiable risk factors in patients with psoriasis could result in a lower associated cardiovascular and metabolic morbidity and mortality. Conceptually, the effective systemic control of inflammation in psoriasis could lead to improvement in co-morbid conditions driven by inflammation [17].

High prevalence of DM in patients with psoriasis has long been recognized. This association was found to be more prominent in women as compared to men and in patients between the ages of 35 and 55 years. In addition, data analysis of
psoriatic patients showed an association between diabetes and the overuse of steroids or certain systemic medications. These observations could indicate that the prevalence of diabetes among psoriatic patients increases with the severity of the disease [18].

It is generally accepted that the emergence of type II DM is preceded by a stage of IGT. Many studies have shown that IGT individuals are resistant to the action of insulin and that the progression from IGT to type II DM is associated with a decline in beta-cell function with additional worsening of peripheral insulin resistance [19]. IR is often considered a central component of metabolic syndrome that significantly increases the risk of cardiovascular morbidity and mortality and plays an important role in the pathophysiology of type II DM [1]. As IR usually develops long before these diseases appear, therefore its identification and treatment has a potentially great preventive value [20].

In our study, we tried to detect the relation between IGT, IR and psoriasis in patients who did not have clinical criteria of metabolic syndrome in order to clarify whether psoriasis itself without metabolic syndrome carries a risk for insulin resistance. The results showed that both fasting and 2h postprandial blood glucose levels were higher in group A than group B with statistical significant difference \( p=0.003 \). Our results are in agreement with previous findings of Grzybowski and colleagues in 2001 who found significant high serum glucose levels in 12 psoriatic patients compared to 15 controls [21]. However, Brenelli and colleagues in 1995 found contradictory results when they applied an oral glucose tolerance test (OGTT) on 10 psoriatic patients and 11 control subjects; found no significant differences in mean plasma glucose levels between patients and normal individuals [22]. Our study showed that 33.3% of our psoriatic patients had IGT which was in agreement with previous findings by Ucak and colleagues in 2007, which included 46,095 patients case-control study that was done by Jonathan and colleagues in 2006, which included 46,095 patients with psoriasis and 1,579,037 controls, who reported significant high serum glucose levels in 12 psoriatic patients compared to 15 controls [23]. However, Boehncke and colleagues studied thirty nine psoriatic patients, observed a significant correlation between the PASI score and both insulin secretion and insulin resistance as measured by HOMA-IR and serum resistin levels; a cytokine known to be increased in IR [25].

Although the mean fasting serum insulin level showed no significant differences between our both groups, yet on applying the cut-off value of 13g U/ml on our cases, we found that 16.7% of cases had fasting serum insulin levels greater than 13g U/ml which was statistically significant \( (p=0.052) \) when compared to controls. This suggests that IR (as regards fasting insulin) was detected in cases more than controls. This agrees with previous findings of Ucak and colleagues in 2006 who used the same cut off value of fasting insulin for IR and they found that 32.9% of their psoriatic patients showed insulin resistance [23].

On the other hand, our work showed that 13.3% of group A had HOMA-IR index greater than 3.2 but was not significantly different when compared to group B. On the contrary, Ucak and colleagues in 2006 found that HOMA-IR index was significantly higher in the psoriasis group than in controls, which might be related to their number of studied patients [22]. On the contrary, Drateln and colleagues in 2003 who estimated IR by using insulin tolerance test (ITT) found no significant difference in insulin sensitivity in psoriasis cases compared to controls [24].

In this study IR was higher in psoriatic cases [16.7%] than controls but no correlation to severity of the disease (measured by PASI score) was detected a finding collaborated by Ucak and colleagues in 2006 who found no significant correlations of both HOMA-IR and HOMA beta-cell indices with PASI score or duration of psoriasis [23]. However, Boehncke and colleagues studied thirty nine psoriatic patients, observed a significant correlation between the PASI score and both insulin secretion and insulin resistance as measured by HOMA-IR and serum resistin levels; a cytokine known to be increased in IR [25].

This study showed that 16.7% of patients in group A had IR with beta cell hypersecretion and compensatory hyperinsulinaemia, where as, 33.3% had IGT with decline in beta cell function (one of them had IR) therefore, 46.6% of patients carry diabetogenic risk.

Both fasting serum insulin levels and insulin resistance in our study were higher in female cases with statistically significant difference when compared to males. This suggests that psoriatic females may carry a higher diabetogenic risk. Our findings are supported by the results of a retrospective case-control study that was done by Jonathan and colleagues in 2007, which included 46,095 patients with psoriasis and 1,579,037 controls, who reported...
that the association between psoriasis and DM was more prominent in women as compared to men [26].

**Conclusion:**

The significant increase in the rates of both IGT and IR in psoriasis suggests that psoriatic patients may carry high diabetogenic risk. The fact that our patients did not have clinical criteria of metabolic syndrome leads us to deduce that psoriasis as a disease entity has an association with IR. Thus we recommend that the evaluation of IR and IGT should be done in psoriatic patients routinely, because if detected and managed early, this will have a great impact on the patient’s prognosis leading to decreased incidence of progression to frank DM, as well as, reduction of the risk of other components of IRS. Furthermore, we recommend future studies on a larger scale in order to collaborate the addition of IR and IGT testing to the routine workup of psoriatic patients.

**References**


