Cutaneous manifestations among Egyptian children and adolescents with type 1 diabetes

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Abstract

Background: Although almost all patients with T1DM eventually develop one or more skin manifestations, data on cutaneous manifestations of type 1 diabetes mellitus (T1DM) are scarce. They can be the first presenting sign, or even precede the diagnosis or develop from the long-term effects of diabetes. Objective: To detect the prevalence and spectrum of skin manifestations in children and adolescents with T1DM attending the DEMPU clinic, Cairo University and to investigate the effect of the disease duration on these dermatoses. Subjects and methods: Two hundred twenty-five children and adolescents with T1DM were examined for dermatological problems. Of them, 152 patients who had cutaneous manifestations with T1DM were included in this case-control study, 152 age and sex matched non diabetic patients were included as control group. A detailed dermatological examination was carried out by the dermatology team. Results: The overall prevalence of dermatologic manifestations was 67.56% (152 T1DM patients; 74 males and 78 females). The mean age of the patients was 8.38 ± 3.79 years and the mean diabetes duration was 2.80 ± 2.86 years. Cutaneous adverse effects related to insulin injections were the most common manifestation representing 28.9%, followed by cutaneous infections (bacterial, fungal and viral infections) in 25%, allergic skin diseases in 19.1% and pruritus in 15.1% of patients with T1DM. Conclusion: Broad spectrums of dermatoses are common (67.56%) in Egyptian patients with T1DM. Early referral to the dermatologist helps to detect skin complications of diabetes in these children and is essential for both prevention and management of these conditions.

Introduction

Although the mechanism for many diabetes-associated skin problems remains unknown, the pathogenesis of others is linked to abnormal carbohydrate metabolism, other altered metabolic pathways, atherosclerosis, microangiopathy, neuron degeneration, and impaired host mechanisms.1 It seems that
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Diabetes, similar to other endocrine disorders, may cause some alterations that could be derived from impaired skin homoeostasis. Cutaneous manifestations generally appear subsequent to the development of diabetes but may be the first presenting sign or even precede the diagnosis by many years. The cutaneous findings can be classified into four major groups: (1) skin diseases associated with diabetes, such as scleroderma-like changes of the hand, necrobiosis lipoidica, and diabetic dermopathy; (2) cutaneous infections; (3) cutaneous manifestations of diabetes complications such as neuropathic foot ulcers; and (4) skin reactions to diabetes treatment.

Objective

The objective of this study was to evaluate the prevalence and the spectrum of skin manifestations in children with type 1 diabetes mellitus (T1DM) attending the Diabetes Endocrine & Metabolism Pediatric Unit (DEMPU) clinic, Cairo University, and to assess its relation to disease duration, metabolic control in children and adolescents with type 1 diabetes.

Material and methods

Study population

To assess the prevalence of the cutaneous manifestations in children with T1DM, two hundred twenty-five children and adolescents with T1DM attending the Diabetes Endocrine and Metabolism Pediatric Unit (DEMPU) clinic were examined for dermatological problems between December 2010 and September 2011. Patients were included if they have T1DM, aged less than 18 years. Children with associated other systemic diseases that may have cutaneous manifestations were excluded.

Only one hundred fifty-two patients were found to have cutaneous manifestations with T1DM and were included in this case-control study (group I). They were compared to the control group (group II).

The control group (group II) included one hundred fifty-two age and sex matched patients with cutaneous manifestations with no history of any systemic disease.

Procedure

- All children were subjected to full history taking including age, sex, onset, course, and duration of the present cutaneous lesions, associated diseases, and history of previous skin diseases and in children with T1DM; duration of diabetes, type of insulin therapy.
- A detailed dermatological examination was carried out by a dermatology team and the cutaneous findings were recorded.
- The charts of children with T1DM were reviewed for the previous results of HbA1c in the past year to assess the glycemic control, and thyroid profile, lipid profile and any other available labs to rule out any associated condition that may be associated with cutaneous manifestations.

Statistical analysis

Data were statistically described in terms of mean ± standard deviation (±SD), median and range for quantitative data, or frequencies (number of cases) and percentages for qualitative data when appropriate. Comparison of numerical variables between the study groups was done using Student’s t test for independent samples in comparing normally distributed data and Mann Whitney U test for independent samples in comparing non-normal data. For comparing categorical data, Chi square (c²) test was performed. Exact test was used instead when the expected frequency is less than 5. p values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results

The prevalence of cutaneous manifestations in children and adolescents with T1DM in the study group was 67.56% (out of the two hundred twenty-five children with T1DM, one hundred fifty-two patients had cutaneous manifestations).

Group (I) included 152 children with T1DM and cutaneous manifestations (74 males and 78 females) with a mean age of 8.38 ± 3.79 years (ranging from 1.5 to 15 years). The mean duration of diabetes was 2.80 ± 2.86 years and the mean HbA1c was 8.91 ± 7.96%. Group II (control group) included 152 patients; 58 males (38.2%) and 94 females (61.8%), their mean age was 5.14 ± 2.02 years (ranging from 3 to 15 years). There was no statistical significant difference between the two groups as regards the age and sex (p = 0.122 and 0.091, respectively).

Regarding the spectrum and the distribution of the skin manifestations in group I (children with T1DM), complications of insulin therapy were the most common cutaneous manifestation in patients with T1DM and diagnosed in 44 cases (28.9%). Fig. 1. The most common insulin complication was insulin lipohypertrophy (36/44 cases) followed by bruises at insulin injection sites (6/44 cases), brown pigmentation at insulin injection sites came in the third order (2/44 cases). Cutaneous infections were the second common cutaneous disease in the study group (group I) diagnosed in 38 cases (25%); they included bacterial, fungal and viral infections (Fig. 1). Bacterial infections were diagnosed in 19 cases (12.5%), 6 males and 13 females. Boils, impetigo and acute paronychia were diagnosed in 16, 2, 1 case/s, respectively. Cutaneous fungal infections were diagnosed in 17 cases (11.2%), 3 males and 14 females. The most common cutaneous fungal infections were candidiasis (monilial vulvovaginitis) (11/17) cases followed by tinea versicolor, tinea corporis and tinea capitis in 3, 2 and 1 case/s, respectively. The most common allergic skin disease in group (I) was papular urticaria (12/29) cases followed by pityriasis alba, urticarial and eczema in 11, 4, 2 cases, respectively.

There was no significant difference between children with T1DM and the control group as regards bacterial and fungal skin infections (p = 0.737, 0.565, respectively), (Table 1).
Pruritus, pigmentary disorders and hyperkeratosis of the sole were significantly higher in children with T1DM ($p = 0.000$, 0.034, 0.036, respectively), (Table 1). Viral infections, parasitic infestations, and hair disorders were significantly lower in children with T1DM ($p = 0.023$, 0.001, 0.020, respectively), (Table 1).

As regards sex differences in each cutaneous manifestation in group (I) there was no significant sex difference in children with complications of insulin therapy and pruritus ($p = 0.111$, 0.822, respectively) while, cutaneous bacterial and fungal infections were significantly higher in females compared to males ($p = 0.043, 0.009$, respectively). However, allergic diseases were more common in males ($p = 0.022$). Acne and Hyperhidrosis of hands were observed only in male patients (Fig. 2).

The mean age, diabetes duration, and HbA1c for children with T1DM with different skin manifestations are summarized in Table 2. The mean age for patients with complications of insulin therapy was $9.49 \pm 3.38$, mean duration was $3 \pm 1.59$, and HbA1c was $7.73 \pm 1.41$.

Children with complications of insulin treatment had significantly older age and longer diabetes duration compared to other children with T1DM ($p = 0.02$ and 0.004, respectively) while, there was no significant difference regarding the sex or the mean HbA1c ($p = 0.111, 0.102$, respectively).

Cutaneous bacterial and fungal infections were significantly higher in females compared to males ($p = 0.043, 0.009$, respectively). Patients with T1DM and bacterial infections had significantly younger age compared to other patients with T1DM ($p = 0.015$) while there was no significant difference as regards diabetes duration or HbA1c ($p = 0.015$ and 0.617, respectively). There was no significant difference between patients with T1DM and fungal infections and other children with T1DM as regards age, diabetes duration and HbA1c ($p = 0.091, 0.439$ and 0.701, respectively).

Allergic skin diseases were significantly higher in males than females (20 cases, 68.9% versus 9 cases, 31.1%, $p = 0.022$). Patients with T1DM and allergic skin diseases had significantly younger age compared to other patients with T1DM ($p = 0.015$) while there was no significant difference as regards diabetes duration or HbA1c ($p = 0.015$ and 0.617, respectively). There was no significant difference between patients with T1DM and fungal infections and other children with T1DM as regards age, diabetes duration and HbA1c ($p = 0.091, 0.439$ and 0.701, respectively).

Discussion

The prevalence of cutaneous manifestations in children and adolescents with T1DM in the Diabetes Endocrine and
Metabolism Pediatric Unit (DEMPU) was 67.56%. This agrees with Sawatkar et al. and Pavlovic´ et al., who found a prevalence of 67.8%, 68%, respectively.\textsuperscript{4,3}

This study demonstrated that complications of insulin treatment were the most prevalent cutaneous manifestation among children with T1DM, as they were observed in 28.9% of the study group. This is in contrast to the finding of Kordonouri et al. and Kordonouri et al., who reported a prevalence of 48%. This can be explained by the different mean duration and control of diabetes across the studies.\textsuperscript{5,6}

In this work the patients suffering from cutaneous complications of insulin therapy were significantly older and showed longer duration of diabetes when compared with others not presenting with the same complications. This was in agreement with Omar et al.\textsuperscript{7} Repeated trauma due to the repeated injections in the same site may be behind the development of lipohypertrophy, so to prevent such local skin reaction; insulin-treated patients should be more intensively trained to regularly change injection sites.\textsuperscript{8}

There was no significant difference between the patients with T1DM (group I) and the control group (group II) as regards the bacterial and fungal infections ($p = 0.737$, 0.565, respectively). This agrees with the finding of Pavlovic’, who reported no significant difference between patients with T1DM and the controls\textsuperscript{3} while, it is in contrast to Simone et al., who reported increased susceptibility to infections in

**Figure 2** Prevalence of skin manifestations among males and females with type 1 diabetes. There was no significant sex difference in patients with complications of insulin therapy and pruritus while, cutaneous bacterial and fungal infections were significantly higher in females. Moreover, allergic diseases, pigmented disorders were more common in males. Acne and Hyperhidrosis of hands were observed only in male patients.

**Table 2** The mean age, diabetes duration, and HbA1c in children with diabetes (group I) and different skin manifestations ($n = 152$).

<table>
<thead>
<tr>
<th>Cutaneous manifestations</th>
<th>Age (year) (mean ± SD)</th>
<th>Diabetes duration (years) (mean ± SD)</th>
<th>HbA1c (%) (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complications of insulin Treatment ($n = 44$)</td>
<td>9.49 ± 3.38</td>
<td>3.62 ± 2.78</td>
<td>8.38 ± 2.25</td>
</tr>
<tr>
<td>Cutaneous infections ($n = 38$)</td>
<td>6.76 ± 3.71</td>
<td>3 ± 1.59</td>
<td>7.73 ± 1.41</td>
</tr>
<tr>
<td>Bacterial infections ($n = 19$)</td>
<td>6.42 ± 3.4</td>
<td>2.33 ± 2.17</td>
<td>7.69 ± 1.27</td>
</tr>
<tr>
<td>Fungal infections ($n = 17$)</td>
<td>6.88 ± 3.49</td>
<td>2.08 ± 1.91</td>
<td>8.02 ± 1.57</td>
</tr>
<tr>
<td>Viral infections ($n = 2$)</td>
<td>7 ± 4.24</td>
<td>2.5 ± 0.71</td>
<td>7.5 ± 1.41</td>
</tr>
<tr>
<td>Allergic diseases ($n = 29$)</td>
<td>7.62 ± 4.66</td>
<td>2.2 ± 2.99</td>
<td>7.82 ± 1.5</td>
</tr>
<tr>
<td>Pruritus ($n = 23$)</td>
<td>8.37 ± 2.87</td>
<td>2.72 ± 3.96</td>
<td>8.31 ± 2.17</td>
</tr>
<tr>
<td>Pigmented disorders and nevi ($n = 4$)</td>
<td>11.25 ± 1.5</td>
<td>3.31 ± 2.09</td>
<td>8.27 ± 2.36</td>
</tr>
<tr>
<td>Hyperkeratosis of soles ($n = 4$)</td>
<td>8.5 ± 4.04</td>
<td>2.46 ± 2.26</td>
<td>8.75 ± 3.18</td>
</tr>
<tr>
<td>Hair disorders ($n = 3$)</td>
<td>12 ± 1.73</td>
<td>4.83 ± 3.17</td>
<td>6.36 ± 0.23</td>
</tr>
<tr>
<td>Parasitic infestations ($n = 2$)</td>
<td>8 ± 5.65</td>
<td>0.37 ± 0.17</td>
<td>6.45 ± 0.07</td>
</tr>
<tr>
<td>Acne ($n = 1$)</td>
<td>13</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Keratosis pilaris ($n = 1$)</td>
<td>15</td>
<td>3</td>
<td>6.5</td>
</tr>
<tr>
<td>Rubeosis faciei ($n = 1$)</td>
<td>6.5</td>
<td>4</td>
<td>7.2</td>
</tr>
<tr>
<td>Hyperhidrosis of hands ($n = 1$)</td>
<td>14.5</td>
<td>1.5</td>
<td>8.5</td>
</tr>
<tr>
<td>Acanthosis nigricans ($n = 1$)</td>
<td>10</td>
<td>8</td>
<td>6.9</td>
</tr>
</tbody>
</table>

HbA1c: glycated hemoglobin, SD: standard deviation.
patients with diabetes. This may be due to the regular follow up, the careful medical supervision and the early and prompt treatment of any infection presenting among the children with T1DM.

Viral infections were observed in 1.3% of children with T1DM. Actually, only two diabetic patients presented with warts. Close to our findings were Khurshid et al., who detected viral infections in 2.9% of diabetic patients.

Allergic skin diseases were the third common cutaneous disorder encountered in children with T1DM in this study (19.1%), they occurred in patients with shorter durations of diabetes. The prevalence of eczema among the children with T1DM in this study was 6.9%. This is in contrast to Rosenbauer et al., who found that atopic eczema was significantly associated with a reduced risk of type 1 diabetes.

The classical explanation of that observation is based on the type 1 and type 2 immune response mechanisms. Type 1 responses made up of Th1 cells and cytokine interferon gamma have been implicated in the pathogenesis of autoimmune diseases such as type 1 diabetes. Type 2 responses on the other hand, are mediated via Th2 cells and interleukin 4, 5 and 13 and play a major role in the pathogenesis of allergic diseases and eczema. The classical Th1/Th2 model proposes that Th1 inflammation suppresses the development of atopy whereas Th2 inflammation suppresses the onset or severity of some autoimmune diseases such as type 1 diabetes through a process of counter-regulation. Thus, in accordance with the Th1/Th2 paradigm development of atopic eczema in early childhood could be protective against childhood type 1 diabetes. In this study the patients diagnosed with eczema reported that eczema started after the onset of diabetes. It seems also reasonable to ask whether the inverse relation between childhood eczema and type 1 diabetes in individuals may be explained by genetic factors. Both the HLA genes and polymorphisms in the CTLA4 and PTPN22 genes are important in immune regulation and are plausible candidate genes in atopic disorders as well. On the other hand, Stene et al. demonstrated directly that the established genetic susceptibility loci for type 1 diabetes (CTLA4 and PTPN22), though important in immune regulation and may play a role also in atopic disorders, do not explain the inverse association between childhood eczema and the subsequent risk for type 1 diabetes previously reported.

Despite acanthosis nigricans being a sign of insulin resistance and usually linked to type 2 diabetes, one female patient with T1DM had acanthosis nigricans. This female patient had familial acanthosis nigricans, she was not obese and had family history of acanthosis nigricans. In this study generalized pruritus was highly observed among children with T1DM (15.1%) and was the fourth common cutaneous manifestation found. This makes it an important cutaneous manifestation of T1DM. In accordance with our results, were Najdawi and Faouri, Yamaoka et al., who observed pruritus in 15.1% and 12%, respectively.

Several cutaneous mediators have been suggested to cause pruritus and could be linked to metabolic changes in diabetes. Diffuse persistent pruritus without an identifiable clinical cause (pruritus sine material) as well as forms of prurigo, especially prurigo simplex subacuta are commonly observed in patients with diabetes. Truncal pruritus can be induced by two mechanisms. First, sympathetic dysfunction may cause diminished sweat production and results in a dry skin. A second mechanism could be the damage to sensory c-fibers by diabetic polyneuropathy.

What was skeptical in our work was that non segmental vitiligo was not diagnosed in children with T1DM, though the association between diabetes and vitiligo is well known as diabetes mellitus and vitiligo share a common risk factor of familial predisposition. Diabetes is often present in close relatives of patients with vitiligo and both diabetes and vitiligo are associated with HLADR3 and HLADR4. Moreover both diabetes and vitiligo share a common theory of autoimmunity. This may be due to the relatively small number of patients enrolled in our study.

Conclusion

The prevalence of cutaneous manifestations in children and adolescents with T1DM in the Diabetes Endocrine and Metabolism Pediatric Unit (DEMPU) was 67.56%. Complications of insulin treatment especially lipohypertrophy, were the most prevalent cutaneous manifestation among children with T1DM. Cutaneous infections among children with T1DM came in the second order among the cutaneous disorders. Candidal infections especially monilial vulvovaginitis were the most common fungal infection observed in children with T1DM. Generalized pruritus is a common cutaneous symptom among children with T1DM. Pigmentary disorders and hyperkeratosis of the sole were more prevalent in children with T1DM.

Conflict of interest

The authors declare that they have no competing interests.

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