Diabetes and the skin

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Today's diabetes world is fast-moving and exciting; knowledge is accumulating at an astonishing rate. To help understand the present, however, it sometimes helps to examine the past.

In this installment of *Tattersall's Tales*, Robert Tattersall explores the history behind diabetes-related skin conditions, looking back at key developments with regard to their presentation, prevalence, diagnosis and treatment.

It has been said that one third of patients with diabetes will develop a diabetes-related skin complication during the course of their disease. So, unless you want to bring your local dermatology department to its knees with referrals, you, the diabetologist, need to be able to recognise, and hopefully treat, these conditions.

In 1927, Arthur Greenwood published a study of dermatologic conditions in 500 patients of Elliott Joslin, of whom 25% presented with a history of skin trouble and 11% had a problem at the time of survey (Greenwood,1927). He wrote, "Textbooks on diabetes mention the following complications as commonly present in diabetes, and generally assume these to be due to hyperglycemia; dry skin; pruritus; chronic urticaria; eczema; perforating ulcer; xanthoma diabeticorum." To these he added a whole group of bacterial and fungal infections. According to Greenwood, one person in 15 presented with a history of pruritus (51% with local and 49% with general itching). Nearly 90% of those with local itching were women but, rather coyly, he did not say which part of their body was affected! By 1951, the Pittsburgh dermatologist William Guy denied that general pruritus was a symptom of diabetes, whereas "Pruritus pudendi is another matter" (Guy, 1951). Some conditions mentioned by Greenwood, such as carotenaemia (yellowing of the skin due to excessive vegetable consumption), have disappeared but this is more than compensated for by the emergence of new conditions.

One rather trivial condition is diabetic dermopathy or "spotted leg syndrome". These lesions (dull red macules or papules on the front of the leg) were originally described by Hans Melin of Umeå in 1964, in a research project he had been given by his professor, Nils Törnblom (Melin, 1964). Among 293 adults with diabetes, 65% of men and 29% of women were affected, a sex ratio that has been found in most subsequent studies. The lesions were most commonly found on the shins and hardly ever found on the back of the leg. Melin was not sure what the primary lesion was but, by sequential photography, he showed that lesions healed slowly over several months leaving round atrophic pigmented scars. Patients hardly ever complained of the lesions but, when questioned, usually attributed them to trauma. This seemed unlikely because one third of those studied had sedentary jobs, and Melin could not find similar lesions in footballers. He further showed that hitting the shin with a rubber hammer could not reproduce the condition! Melin may have thought diagnosis of spotted leg syndrome was simple but a 1966 American paper suggested that shin spots needed to be distinguished from Schamberg's disease, purpura annularis telangiestoides, pigmented purpuric lichenoid dermatitis of Gougerot and Blum and angioma serpiginosum of Hutchinson (Danowski et al, 1966). Wow!

A much more unpleasant and intractable condition is necrobiosis lipoidica diabeticorum (NLD), first described in Vienna by Moriz Oppenheim in 1928 and Erich Urbach in 1932 (Michelson and Laymon, 1934). Urbach's patient was a 44-year-old woman treated with insulin since 1926. In 1928, a lesion appeared on her left calf and 1 year later two similar lesions were noted on her left ankle. Early lesions appeared as papules and then changed to plaques. Oppenheim had followed his patient since 1928 and presented her at the Vienna Dermatological Society but his paper reporting initial findings was not published until 1932, by which time she had developed lesions on her buttocks, palms, soles and face, as well as on her arms and trunk. The lesions, which were aptly described by Michelson and Laymon as having "a smooth glistening surface, which looks as if it were covered with a tightly stretched layer of cellophane," are most commonly found on the legs, especially the shins, but 15% also involve the upper body. I had a patient who had a plaque of NLD on her cheek. Women are more commonly affected by NLD than men (at a ratio of 3:1) and NLD can also occur in people without diabetes. Its aetiology is unknown and treatment is generally unsatisfactory. Local and systemic steroids have been recommended but, in my experience, were no good. Excision of the lesions with skin grafting has been recommended but my limited experience, like that of others, is that NLD recurs in the graft.

Because insulin is injected subcutaneously, it is no surprise that it can cause problems in the skin. Lipoatrophy was reported 4 years after the introduction of insulin but by 1929, Harold Avery could only find 21 cases in the literature (Avery, 1929). By the 1950s, lipoatrophy was remarkably common. In the Leeds clinic in 1953, a quarter of men and two thirds of women had it (Paley, 1953). Aetiological factors considered in the literature were repeated trauma, infection, tricresol used as a preservative in insulin, lipase as a contaminant of insulin, the acidity of soluble insulin, and a local allergic reaction. In Boston in 1949, Alexander Marble and Albert Renold repeatedly injected insulin into the groin fat pads of female rats (using saline as a control) and were surprised to find that it caused hypertrophy rather than the atrophy they had expected. They concluded that, "the primary action of insulin at the site of injection is a direct metabolic one, facilitating the synthesis of fat from carbohydrate. Hypertrophy seems to be the primary response of adipose tissue" (Marble and Renold, 1949). Ronald Paley was the first to suggest that lipoatrophy had an immunological cause and ended his paper saying, "By the use of highly purified insulin in new diabetic patients, it should be possible to demonstrate the absence of this complication." This turned out to be the case and, in 1980, my colleagues and I proved the immunological basis of lipoatrophy (Reeves et al, 1980).

Another complication which, like lipoatrophy, appears to be on the wane, is cheiroarthropathy (limited joint mobility). This was originally described by Knud Lundbaek in 1957 (Lundbaek, 1957) and rediscovered by Arlan Rosenbloom in 1974 (Rosenbloom and Frias, 1974). In its typical form it consists of painless contractures of the finger joints so that the palm cannot be laid flat. It is thought to be due to non-enzymatic glycosylation of collagen, and the very strong clinical impression has always been that it occurs in those with the worst glycaemic control. This was confirmed in a longitudinal series in 1998, in which for every 10.9 mmol/mol (1 percentage point) increase in HbA_{1c} there was a 46% increase in the frequency of limited joint mobility (Silverstein et al, 1998). Rosenbloom and colleagues found a four-fold decrease in the prevalence and severity of limited joint mobility in children with type 1 diabetes in Florida between 1978 and 1998, which they attributed to an improvement in overall blood glucose control (Infante et al, 2001).

Although not strictly a cutaneous complication of diabetes, gustatory sweating is a distressing condition. Sweating after eating was first recorded by the physiologist Charles-Édouard Brown-Séquard at a meeting of the Paris Biological Society in 1849, who demonstrated that within minutes of eating chocolate he showed severe facial sweating. Presumably, this was idiopathic but, over a century later, a similar phenomenon was reported following damage to the auriculotemporal nerve in its passage through the parotid gland (Frey's syndrome) or as a result of cervical sympathectomy. Surprisingly, gustatory sweating was not reported in diabetes until 1973, when Peter Watkins of King's College Hospital, London described it in six people with long-standing diabetes and severe, particularly autonomic, complications (Watkins, 1973). In two individuals, sweating was was so severe that sweat poured down the chest at meal times, drenching the shirt, and both had to keep a towel beside them on the dinner table. Watkins found that chewing an inert substance did not cause sweating, and the most potent stimulus was cheese. As with Frey's syndrome, the symptoms of gustatory sweating were thought to be due to abnormal nerve regeneration following autosympathectomy. It can now be treated with anticholinergic drugs, although many people prefer to put up with it rather than endure the side effects of therapy.

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