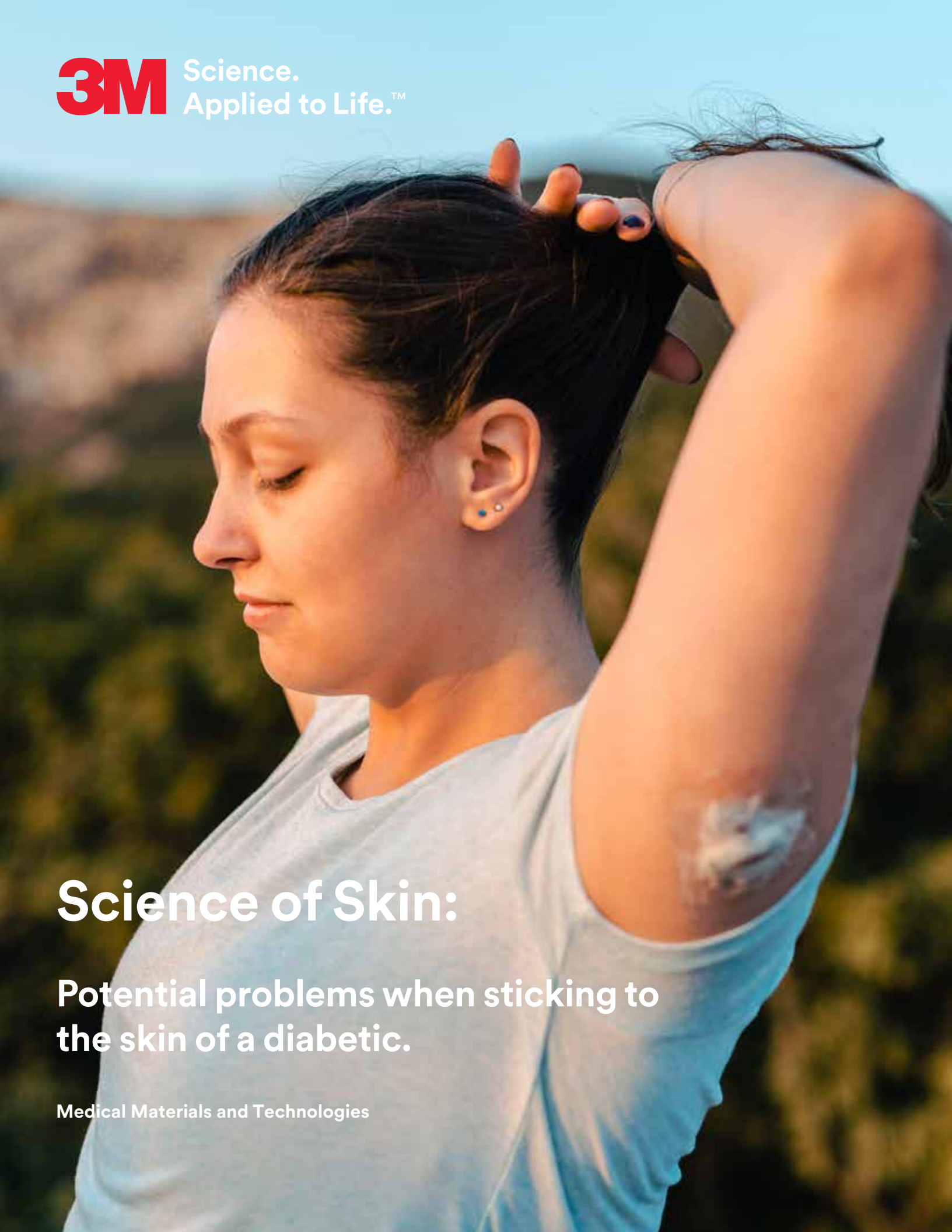

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Science of Skin:

Potential problems when sticking to the skin of a diabetic.

Medical Materials and Technologies

Science of Skin:

Potential problems when sticking to the skin of a diabetic.

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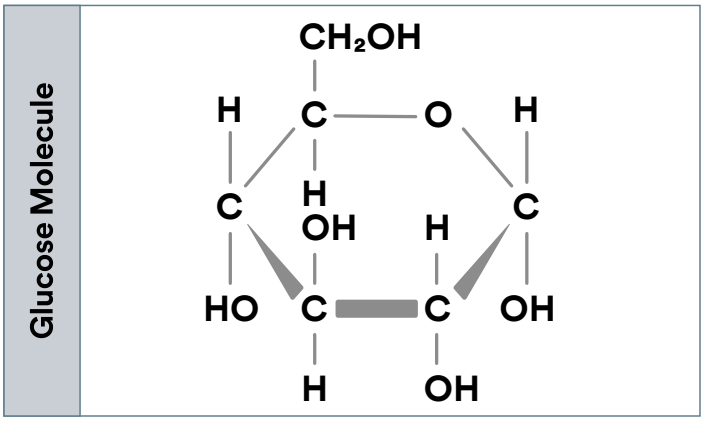
The skin of diabetic patients requires special attention. While there are multiple forms of diabetes, from the viewpoint of the number of individuals with the disorder, diabetes mellitus is the form most commonly associated with the word "diabetes". Diabetes mellitus has a long history of being divided into Type 1 and Type 2 diabetes, although there is increasing overlap between these types as the population with this disorder rises. Historically, Type 1 diabetes is associated with onset during childhood, referred to as "juvenile onset diabetes" and classically is the result of the loss of insulin producing cells in the pancreas. By comparison, Type 2 diabetes has been associated with the concept of being "adult onset diabetes" and commonly is associated with multiple biochemical changes captured in the term "metabolic syndrome". It is common for Type 2 diabetics to be associated with obesity and as the complications of obesity become increasingly recognized, diabetes will be a common endpoint for many patients. The disease process associated with diabetes may involve locally secreted substances that have a "paracrine" effect. However, the critical substance in diabetes and in its management is the hormone insulin. As is the case with any hormone, it is produced at one site, transported through the bloodstream and reacts distally with receptors on the surface of responsive cells. Different abnormalities involving insulin distinguish Type 1 from Type 2 diabetes. Type 1 diabetics fail to produce insulin and require exogenous insulin for treatment. Type 2 diabetics can produce insulin but fail to produce enough insulin and tend to release it at a rate too slow to maintain normal blood glucose levels after an oral glucose load. Both the diagnosis and the treatment of diabetes focuses on the measurements of blood glucose levels. Well established clinical guidelines provide the parameters used to determine the presence of diabetes and its precursor form, "pre-diabetes". Irrespective of origin, however, both Type 1 and Type 2 diabetics will suffer from an elevated blood glucose level and the degree of damage to the body, and the skin, will reflect the magnitude and duration of these elevated glucose levels.



Damage to the skin because of diabetes is like other adverse events involving the skin since abnormalities will compound in an additive way to already existing changes. For example, it is a well-recognized phenomenon that aging skin will be less resilient to external stresses[1]. Intrinsic aging of the skin will be reflected in a loss of elasticity of the dermis and fine lines will appear on the skin surface. Extrinsic aging caused by prolonged exposure to the sun will convert fine lines into deep coarse wrinkles[2]. The abnormal glucose metabolism that accompanies diabetes will exacerbate these problems.

In normal glucose metabolism, a glucose load that accompanies

food ingestion is followed by the rapid release of insulin, binding of the hormone to receptors and the rapid uptake of glucose into the cells. In diabetes, irrespective of type, the glucose can remain in the bloodstream for an extended time. If the glucose levels reach a critical threshold, glucose can appear in the urine. If the glucose becomes elevated to an even greater degree, hyperosmolar coma can result. The failure to properly use glucose will result in an effort to use other sources of energy, such as amino acids or fats. The metabolism of these compounds, instead of glucose, can result in excessive keto acids and can result in the life-threatening condition of diabetic ketoacidosis. To avoid any and all of these complications, patients will receive varying amounts of insulin with different lifetimes in the bloodstream. Type 1 diabetics require exogenous insulin while Type 2 diabetics are treated with alternative medications but may also use exogenous insulin injections as well.

When we consider the role of glucose in diabetics we must include a wide range of potential problems in the skin, from pH abnormalities due to acidosis to the primary issue of improperly managed blood glucose. Excess blood glucose could combine with the skin directly, a process referred to as "non-enzymatic glycosylation". The non-enzymatic reaction of glucose with

blood vessel walls results in stiffening of the blood vessel wall, subsequently reflected in accelerated atherosclerosis. In the skin, the small vessels may fail to respond normally to stimuli, leading to decreased or abnormal oxygen and metabolite exchange. A long-term effect is the loss of sensory nerve cells within the skin. This lack of sensation can result in undetected injury since pain fibers are absent and the stimulus to withdraw from the source of pain is lost. Excess glucose predisposes to increased urination which can dry the skin. Loss of neurons due to diabetes can lead to loss of sweat gland function in the skin. Together, to varying degrees, these events result in the skin of diabetics being abnormally dry and xerosis is a characteristic feature of diabetic skin. Xerosis is quite common among diabetics and typically is seen in combination with itching (pruritus) and thickening of the skin, reflecting the broad scope of non-infectious adverse events involving the skin that can accompany diabetes[3].

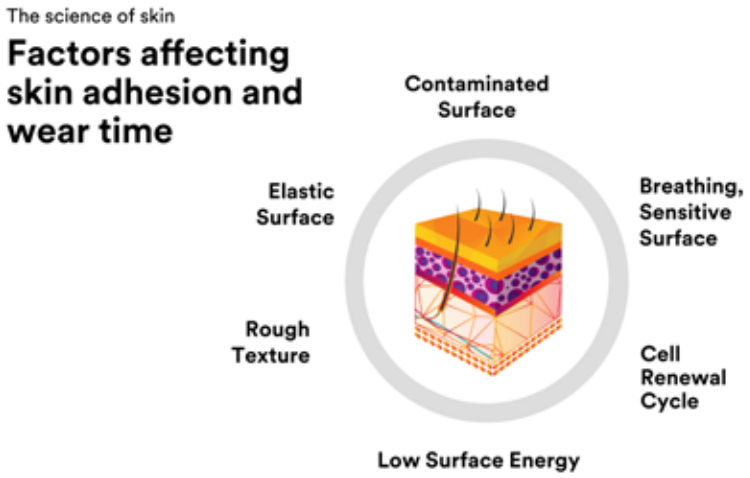
The non-enzymatic glycosylation results in “advanced glycation end products”, commonly referred to as AGEs. AGEs can accumulate in the skin and the degree of autofluorescence of the skin correlates with the amount of AGEs present[4]. These AGEs cause an immune imbalance that effects the skin in what appears to be paradoxical ways. First, they induce a chronic inflammatory condition. Second, they interrupt the normal process of healing by leading to an understated healing response[5]. Additionally, diabetics have a well-established reputation for increased skin and soft tissue infections[6] resulting from an altered immune response[7]. These infections are of concern because skin breakdown can serve as an entry point for pathogenic micro-organisms[8]. Unfortunately, the degree of immune defects in diabetics also predisposes them to infections by atypical organisms.

The risks of infection inherent in diabetic skin because of the loss of integrity of the skin are magnified by the use of devices that both monitor blood glucose levels or deliver insulin to the patient. Injury to diabetic skin can result in skin and soft tissue infections and the use of continuous glucose monitors (CGM) may contribute to the risk. As considered previously, the effects of excess glucose are cumulative. It is recognized that the time during which the glucose levels are raised help to determine the long-term abnormalities than can result.

The use of CGM carries great clinical value since it can help to maintain short term levels of glucose in a normal or near normal range, reducing the probability of long-term effects as well[9]. The challenges associated with the use of CGM reflect demographics as well as technology: the benefits accrue most to Type 1 young diabetics, those known to be most difficult to maintain glucose control[10].

Irritation, not associated with infection, can also occur. Irritation is expressed most frequently as skin rash particularly in those patients where either a CGM or infusion pump is being used for an extended time. The use of continuous subcutaneous insulin infusion may provide closed loop control of glucose levels, but the presence of a catheter that breaches the skin barrier brings with it its own increased risk of infection in a susceptible population. It is not unusual that catheter related, and site related adverse events can occur two to three days after placement and may include itching, bruising, swelling and pain, independent of catheter related problems such catheter infection[11]. The frequency of allergic reaction is unclear: under-reporting or under appreciation may hide a higher frequency of events[12].

The ability to maintain glucose levels near or within normal limits carries great promise in reducing the long-term complications associated with diabetes mellitus. As is the case with all technologies, a balance between the skin and the device must reflect the underlying biological condition to maximize benefit with a minimum of complications.



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