

# Association of tanning injection with hypercortisolism, hyperglycaemia and ketosis in type 1 diabetes mellitus

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**Key words:** tanning injection (Melanotan 2), hypercortisolism, hyperglycaemia, ketosis, type 1 diabetes mellitus

## Abstract

A 39-year-old man with type 1 diabetes mellitus (T1DM) presented with vomiting, hypertension, a tanned appearance, diabetic ketosis without acidosis, and hypercortisolism. It was found that he had been using TruTan (Melanotan 2) for a prolonged period. Melanotan 2 is a non-selective melanocortin-receptor agonist that induces skin and hair pigmentation but also has the potential to cause side effects such as nausea, vomiting, weight loss, spontaneous penile erections and increased sexual arousal. This case report highlights the potential for endocrine and metabolic complications associated with the unlicensed use of TruTan (Melanotan 2), in people with T1DM, emphasizing the need for awareness of these risks in clinical practice.

## Introduction

The melanocortin system is a complex family of peptide hormones derived from the pro-opiomelanocortin (POMC) precursor through limited proteolysis and post-translational modifications.<sup>1</sup> The major members of this family include adrenocorticotrophic hormone (ACTH), melanocyte-stimulating hormones ( $\alpha$ -MSH,  $\beta$ -MSH and  $\gamma$ -MSH),  $\beta$ -endorphin and  $\beta$ -lipotropic hormone ( $\beta$ -LPH). The main source of POMC is the pituitary gland. However, POMC mRNA is also found in other brain structures, as well as in peripheral organs such as lymphocytes, skin, placenta, pancreas, thyroid gland, testes, intestines, kidneys and liver.<sup>2</sup> The peptides of the melanocortin family are involved in a wide range of physiological processes,

including skin pigmentation, stress responses and energy regulation. Among them,  $\alpha$ -MSH plays a central role in melanin synthesis, resulting in skin pigmentation.<sup>3</sup>

The melanocortins activate five different subtypes of melanocortin receptors (MCRs), including MC1R, MC2R, MC3R, MC4R and MC5R.<sup>4</sup> Each receptor, with distinct tissue distributions, is responsible for different physiological functions. MC1R is responsible for skin and hair pigmentation through regulating the melanin production in melanocytes. MC2R is involved in steroidogenesis in the adrenal cortex. MC3R and MC4R are important in the regulation of food intake, eating behaviour and energy expenditure, contributing to changes in appetite and weight.<sup>4,5</sup> MC4R is also involved in the regulation of sexual desire.<sup>6</sup> MC5R is primarily involved in the function of exocrine glands.<sup>4</sup>

Synthetic melanocortin analogues, such as Melanotan 1 and Melanotan 2, collectively known as melanotans, have been used by some individuals to obtain a cosmetic skin tan, though they are unlicensed and unregulated.<sup>7</sup> These melanotans are potent non-selective MCR agonists that mimic the action of  $\alpha$ -MSH. Their action on MC1R induces skin tanning. However, their non-selective activity across other MCR subtypes can cause a wide range of physiological effects.<sup>8</sup> The direct ACTH-like effect of melanotans on MC2R could increase cortisol levels.<sup>9,10</sup>

Short-term use of melanotans is known for minor side effects such as facial flushing, nausea, vomiting, fatigue and changes in naevi, particularly melanocytic changes in existing moles and newly emerging dysplastic naevi.<sup>11,12</sup> Their non-selective MCR binding can lead to serious side effects including priapism, hypertension, melanoma, melanonychia, rhabdomyolysis, renal failure, renal infarction and posterior reversible encephalopathy syndrome, especially with prolonged use.<sup>13-15</sup> We present a male patient with T1DM who developed diabetic ketosis without acidosis, vomiting and hypercortisolism after using TruTan (Melanotan 2) injections for an extended period. This case may raise awareness of the potential endocrine complications associated with unlicensed tanning injections, particularly in individuals with T1DM.

## Case presentation

A 39-year-old male with T1DM since 2007 presented because he had been vomiting for three days. On clinical assessment, he was found to be hypertensive and he exhibited an unduly tanned appearance of his entire body. Biochemical tests revealed diabetic ketosis without acidosis, with a pH of 7.388,

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capillary blood glucose of 41 mmol/L, ketones of 4.2 mmol/L and HbA<sub>1c</sub> of 85 mmol/mol. Additionally he had hyponatremia, with a sodium level of 128 mmol/L.

The patient was treated with proton pump inhibitors, anti-emetics, intravenous fluids and a variable-rate insulin infusion (VRII) regimen. He was referred to the endocrine team, and primary adrenal insufficiency was initially suspected due to the combination of hyponatremia and hyperpigmentation. However, further investigation revealed unusually high cortisol levels (>1,750 nmol/L) along with ACTH at 94 pg/mL. Notably, the patient had never received any form of exogenous steroids and had no clinical signs typical of Cushing’s syndrome, although his blood pressure remained elevated at 176/107 mmHg.

Further questioning revealed that the patient had been using TruTan (Melanotan 2) injections for the past five years to maintain a tanned appearance. He administered Melanotan 2 (0.2 ml, equivalent to 2 mg) once a week for 2-3 weeks before holidays, typically a few times a year for the past five years. His most recent injection occurred five days before admission. On repeat testing, it was noted that his cortisol levels decreased from >1,750 nmol/L to 1,460 nmol/L the following day; within three days they normalised to 441 nmol/L. Similarly, his ACTH levels fell from 94 pg/mL to 15 pg/mL over the same period.

In our hospital, ACTH levels are measured using the Roche Cobas 8000 analyzer with the Elecsys ACTH assay. It is important to note that exogenous hypercortisolism would

typically result in low ACTH levels. We concluded that the elevated ACTH observed in this case was probably due to cross-reactivity of the ACTH assay with Melanotan 2 after an MDT discussion with a consultant biochemist. The Elecsys ACTH assay is known to cross-react with the POMC precursor,<sup>16</sup> although no articles have specifically reported Melanotan 2 directly interfering with the assay.

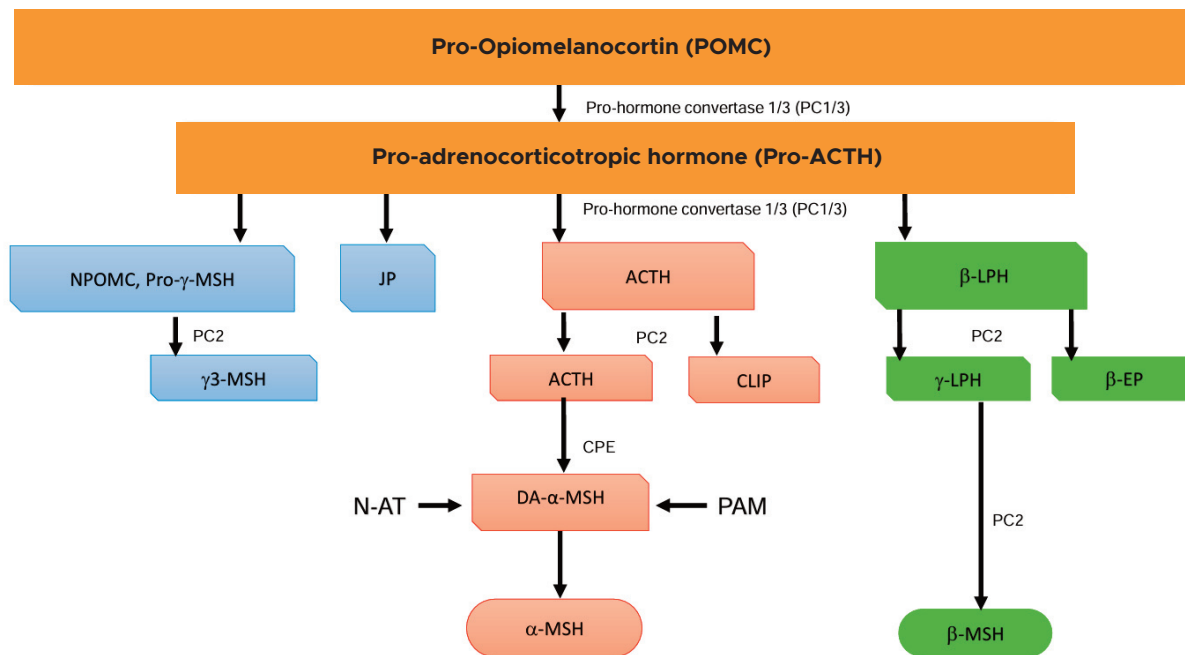
An Endocrine multidisciplinary team (MDT) agreed on the diagnosis of exogenous hypercortisolism induced by TruTan (Melanotan 2) leading to impending diabetic ketoacidosis (DKA). Given the resolution of the patient’s symptoms and biochemical markers, further investigations for Cushing’s syndrome were deemed unnecessary. The patient was strongly advised to discontinue TruTan and other tanning preparations.

A limitation of this case report is the absence of testing for blood concentrations of Melanotan 2 or its metabolites at admission. While Melanotan 2 can be detected using liquid chromatography and mass spectrometry, such testing is not routinely available. Therefore, direct confirmation of Melanotan 2 levels could not be performed in this case.

**Discussion**

Synthetic melanocortin analogues, Melanotan 1 (linear peptide) and Melanotan 2 (cyclic truncated peptide), are more than 1,000 times more potent than endogenous α-MSH.<sup>17</sup> Melanotan 1 is approved in the name afamelanotide by the EMA, the US FDA and the Australian TGA for the treatment of erythropoietic

**Figure 1.** Melanocortin physiology



Key: POMC = pro-opiomelanocortin; PC1/3 = pro-hormone convertase 1/3; CPE = carboxypeptidase E; PAM = peptidyl-glycine α-amidating monooxygenase; N-AT = N-acetyltransferase; ACTH = adrenocorticotrophic hormone; CLIP = corticotropin-like intermediate peptide; MSH = melanocyte-stimulating hormone; β-LPH = β-lipotrophic hormone; β-EP = β-endorphin

protoporphyrin. The other two  $\alpha$ -MSH analogues that are approved for medical indications include bremelanotide, a cyclic heptapeptide approved by the US FDA for the treatment of hypoactive sexual desire disorder in women; and setmelanotide, a cyclic octapeptide approved by the US FDA for the treatment of monogenic or syndromic obesity.<sup>2</sup> Afamelanotide is a selective MC1R agonist. Bremelanotide, which is derived from Melanotan 2, acts primarily on MC3R and MC4R. Though it also has some effects on MC1R and MC5R, it spares MC2R.<sup>17</sup> Setmelanotide (a selective MC4R agonist) has around 20-fold enhanced selectivity towards MC4R versus MC3R.<sup>18</sup>

TruTan (Melanotan 2) is an unlicensed drug that is widely used to get a tanned appearance, often in anticipation of holidays (as in our case) or body-building competitions.<sup>19</sup> It is also used to induce penile erections and increase sexual desire.<sup>8</sup> Melanotan 2 mostly binds to MC1R to increase skin tanning. However, it also binds to MC2R to increase cortisol production from the adrenal cortex, causing clinical hypercortisolism, resulting in elevated blood pressure and blood sugar levels.<sup>10</sup>

The combination of severe vomiting, dehydration and hyperglycaemia might have triggered the onset of diabetic ketosis. Fortunately, DKA did not develop, though he was in impending DKA. The hypertension from hypercortisolism was particularly problematic, as his blood pressure remained elevated despite treatment. It is important to note that he used Melanotan injections over an extended period; however, its administration was intermittent rather than continuous. This

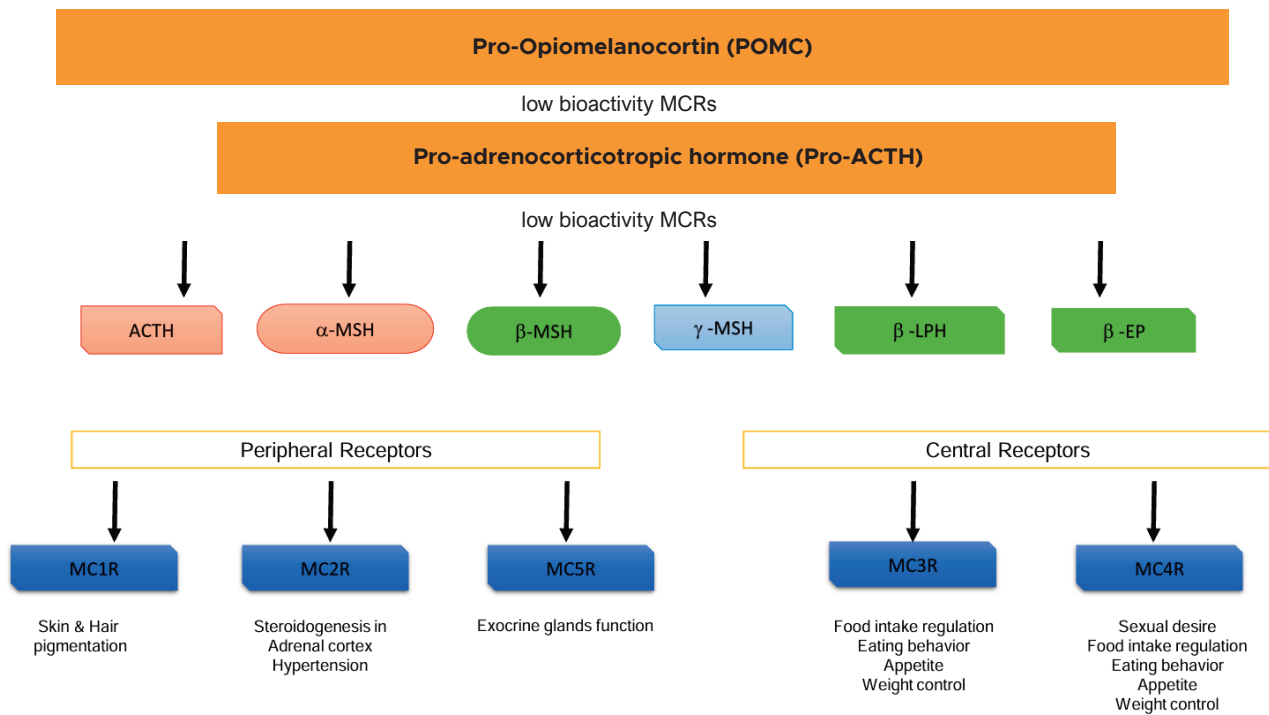
pattern of use may explain the absence of clinical features typically associated with chronic hypercortisolism. The symptoms presented are more likely attributable to recent post-injection side effects. Exogenous hypercortisolism usually causes low ACTH levels. However, the ACTH levels were markedly raised in our case. The ACTH assay can sometimes cross-react with Melanotan 2, as seen in this case. The raised ACTH levels even in the presence of exogenous hypercortisolism suggest that the assay might have detected the Melanotan 2 peptide as if it were ACTH.

Healthcare professionals need to be aware of the broader physiological effects of these agents and to consider them in their differential diagnosis when patients present with unexplained symptoms such as hypertension, hyperpigmentation, vomiting and diabetic ketosis. The use of TruTan and similar substances should be carefully scrutinized, particularly in individuals with diabetes mellitus. While TruTan-related complications such as rhabdomyolysis, systemic toxicity with sympathomimetic symptoms, renal dysfunction and posterior reversible encephalopathy syndrome are concerning,<sup>7,14</sup> the risks in patients with diabetes mellitus can be particularly severe and life-threatening.

**Conclusion**

The use of Melanotan 2 (TruTan), while marketed for cosmetic purposes, can lead to significant endocrine complications. In this case, the exogenous hypercortisolism induced by Melanotan 2

**Figure 2.** Effects of different melanocortin hormones



Key: POMC = pro-opiomelanocortin; MCR = melanocortin receptors; ACTH = adrenocorticotrophic hormone; MSH = melanocyte-stimulating hormone;  $\beta$ -LPH =  $\beta$ -lipotropic hormone;  $\beta$ -EP =  $\beta$ -endorphin;



### Key messages

- ▲ Broad Side Effects: Melanotan can cause both minor (e.g., nausea, flushing) and severe effects (e.g., hypertension, hypercortisolism, renal failure).
- ▲ Diagnostic Awareness: Healthcare professionals should consider melanotan use in differential diagnoses for unexplained symptoms such as hypertension, vomiting and diabetic ketosis, especially in diabetic patients
- ▲ Endocrine Risk: Unlicensed substances like Melanotan 2 can significantly disrupt endocrine function, potentially worsening conditions like type 1 diabetes through mechanisms like exogenous hypercortisolism, leading to serious metabolic crises.

exacerbated the patient's T1DM, contributing to hypertension, hyperglycaemia and impending diabetic ketoacidosis. This case highlights the need for increased awareness and caution regarding the use of unlicensed substances and their potential adverse effects on endocrine function.



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**Declaration** Informed consent was obtained from the patient for this case report.

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