Could Overt Diabetes Be Triggered by Abuse of Selective Androgen Receptor Modulators and Growth Hormone Secretagogues? A Case Report and Review of the Literature

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Case Presentation

In October 2018, a 47-year-old male recreational bodybuilder presented to his general practitioner in Prague, Czech Republic, with polydipsia (daily fluid intake 5–6 L), polyuria, blurred vision, malaise, and weight loss of 10 kg in the past month. He did not complain of any pain or fever and was taking no regular medication except recent (3 months) use of performance-enhancing drugs (PEDs) purchased from a fitness center, including two selective androgen receptor modulators (SARMs)—RAD140 5 mg twice daily and andarine 25 mg twice daily, 5 days per week—as well as the growth hormone (GH) secretagogue (GHS)/ghrelin analog ibutamoren 25 mg daily, 5 days per week. He had no previous use of hormonal supplements.

The patient reported no serious disease apart from borreliosis in 2012, seasonal pollinosis, and minor injuries related to physical activities. Three years before this visit, he underwent a routine general check-up. At that time, his weight was 109 kg, height was 180 cm, and calculated BMI was 33.6 kg/m^2. Laboratory tests revealed impaired fasting glucose (IFG), although the patient was not sure if he was fasting before sampling, as well as hepatopathy (elevated aminotransferases and liver steatosis on abdominal ultrasound scan), hyperuricemia, and dyslipidemia (Table 1). Regarding his family medical history, both parents were obese, his mother was diagnosed with diabetes at the age of 50 years (treated with oral hypoglycemic agents), and there was no available information about his grandparents. The patient had no siblings, and his only daughter was healthy.

Upon examination, he was fully coherent, alert, and oriented and displayed no signs of hyperventilation or dehydration. His physical appearance suggested intensive physical activity. His capillary blood glucose (Accu-Chek; Roche, Basel, Switzerland) was 558 mg/dL (31 mmol/L), weight was 102.7 kg, and BMI 31.7 kg/m^2. His blood pressure was 150/100 mmHg.

Initial blood work (Table 1) confirmed hyperglycemia, high A1C, and dyslipidemia. Urinalysis showed high glucose and no ketones. Thyroid function was normal. Subsequent tests showed no GAD or insulinoma-associated protein 2 (IA-2) antibodies.

The patient was immediately referred to a diabetes care unit, where insulin therapy was initiated. He refused hospitalization but accepted intensive insulin therapy (glulisine and glargine) and cessation of PEDs. He was given a glucose meter and was instructed on blood glucose monitoring, diet, and insulin management. His clinical status, glucose profile, adherence to the diet, and insulin self-adjustment according to carbohydrate intake protocols were reviewed the next day and then at 1- to 4-week intervals.

During the first week, his glycemic profile improved (Table 2). His body composition (Tanita body composition analyzer; Tanita Corporation, Arlington Heights, IL) was as follows: weight 104.8 kg, lean body mass (LBM) 79.4 kg (75.8%), and total fat 21.4 kg (20.4%) (Table 3).

At week 2, the patient underwent laboratory work after omitting glargine the night before sampling. His fasting plasma glucose was 150 mg/dL (8.3 mmol/L), with values for insulin (11.3 mU/L, normal range 3.0–25.0)

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TABLE 1 Historical, Initial, and Follow-Up Biochemistry

	Previous Results*	Initial Values†	6 Weeks‡	12 Months‡	Reference Range
Glucose, mg/dL	103	571	126	113	70–99
A1C, %	–	13.9	8.6	5.6	4.0–6.0
Total cholesterol, mg/dL	201	259	193	205	112–193
LDL cholesterol, mg/dL	109	188	136	121	46–116
HDL cholesterol, mg/dL	36	31	39	47	39–81
Triglycerides, mg/dL	278	587	263	186	40–150
Uric acid, mg/dL	7.3	4.6	6.1	–	3.4–7.0
Creatinine, mg/dL	1.16	1.22	1.06	–	0.70–1.20
eGFR–CKD-EPI, mL/min/1.73 m^2	74	70	83	–	60–180
CRP, mg/L	0.4	0.6	–	–	0.0–5.0
Bilirubin, mg/dL	0.6	–	0.4	0.4	0.0–1.2
ALT, units/L	65	–	60	55	6–40
AST, units/L	45	–	27	34	6–40
ALP, units/L	84	–	88	78	40–131
GGT, units/L	34	–	56	48	10–70
Pancreatic amylase, units/L	–	–	71	39	17–66
Lipase, units/L	–	–	72	54	0–60
TSH, mU/L	1.70	2.11	–	–	0.27–4.20
Free thyroxine, ng/dL	1.3	1.2	–	–	0.9–1.7
LH, IU/L	–	–	3.1	2.3	1.6–9.0
FSH, IU/L	–	–	2.4	3.7	1.4–15.1
Total TST, ng/dL	–	–	160	286	209–800
Free TST, %	–	–	46.4	–	35.0–92.6
Free TST, ng/mL	–	–	–	0.94	0.83–2.06
Estradiol, pg/mL	–	–	10.7	20.2	11.2–40.2
SHBG, μg/dL	–	–	0.33	0.43	0.41–1.77

*From general practitioner check-up 3 years before hyperglycemia manifestation. †Values at initial presentation. ‡Values after quitting PEDs and under antidiabetic treatment. ALP, alkaline phosphatase; CRP, C-reactive protein; eGFR–CKD-EPI, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration formula; FSH, follicle-stimulating hormone; GGT, γ-glutamyltransferase; LH, luteinizing hormone; TSH, thyroid-stimulating hormone; TST, testosterone.

and C-peptide (2.1 ng/mL, normal range 0.8–3.7) within the reference limits. The corresponding homeostatic model assessment for insulin resistance (HOMA-IR) value was 4.18.

At week 3, his glycemic profile further improved (Table 2), and he was able to discontinue glulisine. Metformin 500 mg twice daily was introduced in combination with glargine.

TABLE 2 Blood Glucose Monitoring Data (mg/dL) with Intensive Insulin Therapy During the First 3 Weeks After PED Cessation

Day	Breakfast		Lunch		Dinner	
	Before	2 Hours After	Before	2 Hours After	Before	2 Hours After
1	283	409	321	324	285	288
6	211	169	115	148	135	178
21	139	103	106	144	128	97

Patient was asked to quit PEDs at presentation and did not report taking any PEDs thereafter. Intensive insulin therapy included glulisine and glargine.

At week 6, the patient's metabolic status showed continued improvement (Table 1), but pancreatic and hepatic irritation was found. An abdominal ultrasound showed persistent diffuse hepatic steatosis and a normal pancreas. Sex hormone testing revealed low sex hormone–binding globulin (SHBG), total testosterone, and estradiol but normal values of free testosterone and gonadotropins. Ophthalmology exam excluded diabetic retinopathy.

At week 10, his weight was 108.1 kg, LBM was 79.8 kg (73.8%), and fat mass was 24.2 kg (22.4%) (Table 3). Fasting blood glucose (FBG) was consistently <124 mg/dL (6.8 mmol/L) on only 8 units of glargine. Subsequently, glargine was ceased, and the patient continued treatment only with metformin 500 mg twice daily.

Meanwhile, the patient progressively resumed his regular, high-volume physical activity combining resistance training (1.25 hours daily in his fitness center) with endurance activities such as 3-hour volleyball matches, running 6–7 km, cycling 40 km, or in-line skating 25 km several times per week. He gradually regained 5 kg and his self-estimated former level of physical performance.

TABLE 3 Changes in Body Composition from Week 1 to Week 10

	Week 1	Week 10
Height, cm	180	–
Weight, kg	104.8	108.1
BMI, kg/m^2	32.3	33.4
Lean body mass, kg	79.4	79.8
Lean body mass, %	75.8	73.8
Fat mass, kg	21.4	24.2
Fat mass, %	20.4	22.4

During the next 10 months, his FBG remained between 108 and 126 mg/dL (6.0–7.0 mmol/L).

One year after presentation, IFG, dyslipidemia, and mild hepatopathy persisted. His HOMA-IR improved (3.60), and his A1C, pancreatic enzymes, and sex hormones reached normal limits (Table 1).

Questions

1. Was the sudden deterioration of glucose control in this case a consequence of PED abuse?
2. If so, what mechanisms may have been involved?

Commentary

Overview of SARMs and GHS/Ghrelin Analogs

PEDs are compounds that are illicitly used to increase muscle mass and strength and reduce fat mass. The first representatives were testosterone and its derivatives (anabolic steroids) (1). Subsequently, the range has expanded to new classes, including SARMs and GHSs, which were shown to have some promising effects (in humans and/or animals) during pharmaceutical development. Originally, testosterone and anabolic steroids were secretly abused by elite athletes, but their use gradually spread to the general population (1,2). Currently, some PEDs can be easily procured as veterinary products (e.g., trenbolone acetate) in the United States and many other countries (3), but supplies are obtained mainly from illicit sources through dealers, in fitness centers, and via the internet (1,4–6). Although many PEDs are or include hormones, they are aggressively marketed as dietary supplements (7). As a result, they circumvent rigorous studies required for approval by the U.S. Food and Drug Administration (FDA) (1,2).

Although the prevalence of androgenic steroid abuse is well documented (2,8), the extent to which other PEDs are used is largely unknown (1,7). A study assessing the situation in the United States in 2016 found that, of 44 products marketed and sold via the internet as SARMs, 52% contained one or more SARM, 39% contained another unapproved drug, 45% were sold as dietary supplements, and 55% were labeled "for research use only," "not for human consumption," or both (7).

To induce desired changes in body composition and performance, two major pathways are used: activation/modulation of androgen receptor activity and GH/insulin-like growth factor-1 (IGF-1) axis.

Testosterone represents the mainstay of the first approach because of its anabolic actions on muscles and the skeleton at the expense of its deleterious effects on the reproductive system. To attenuate these impacts, many anabolic steroids have been developed (1). The side effects of these drugs—polycytemia, hepatotoxicity, and debated cardiovascular effects—are other concerns (1,2,9), as well as deterioration of glucose metabolism associated with higher insulin resistance (IR) and visceral adipose tissue accumulation (10,11).

RAD140 and andarine are SARMs (i.e., nonsteroidal molecules) with affinity to androgen receptors as high as that of testosterone (12) and a larger dissociation between anabolic and androgenic properties than that of anabolic steroids. The molecular mechanism responsible for the tissue specificity of SARMs has not yet been clarified, but conformational changes in androgen receptor molecules distinct from those induced by testosterone binding, recruitment of different spectra of coactivators/corepressors (13), and resistance to metabolization have been proposed (1,14).

Preclinical studies have indicated anabolic properties of several SARMs (15), as well as some neuroprotective (16) or anticancer (14) effects. However, only a few SARMs have advanced to clinical testing in humans. Short-term studies tested three compounds—enobosarm (GTx-024, Memphis, TN), GSK2881078 (GlaxoSmithKline, London, U.K.), and LGD-4033 (Ligand Pharmaceuticals, San Diego, CA)—with the results suggesting effects on muscle mass and some indices of muscle strength in healthy people or in patients with cancer (17–20). Side effects included decreased SHBG and total testosterone. All three SARMs decreased HDL cholesterol and triglyceride levels. An increase in LDL cholesterol was shown in a study of GSK2881078 (20). The impact on glucose metabolism was generally neutral (21), although an enobosarm trial suggested some improvement in glucose control and IR (17).

The second approach is to activate the GH/IGF-1 axis. It is well established that GH promotes anabolism and increases LBM, stimulates lipolysis, and reduces fat mass (22). In excess, GH induces glucose intolerance and diabetes by reducing insulin sensitivity and glucose uptake in adipose tissue and muscle (23) and by increasing hepatic glucose production (22).

GH production and secretion can be stimulated by ligands acting through the GHS/ghrelin receptor. An endogenous ligand of the receptor is ghrelin (24,25). In addition to releasing GH, it regulates food intake and energy homeostasis and influences lipid metabolism and glucose homeostasis (26). Indeed, ghrelin directly and indirectly (by stimulation of somatostatin release from δ-cells in the pancreas) inhibits insulin secretion and alters insulin sensitivity in animals and humans (26).

Several GHS/ghrelin receptor ligands such as ibutamoren have been synthetized. Ibutamoren is a nonpeptidic GHS with high oral bioavailability and a long half-life (4.7 hours) (27). It was tested for the treatment of childhood-onset GH deficiency in both children (28) and adults (29). Ibutamoren (5–50 mg daily) was also tested for anabolic indications in humans. Despite evidence of the resulting significant increases in GH, IGF-1, and LBM, studies did not provide compelling evidence of benefits in most functional measures (e.g., muscle strength and stair-climbing power) or effects on bone or total or visceral fat mass (30–33). However, a consistent adverse effect of ibutamoren was glucose tolerance deterioration demonstrated by FBG, 75-g oral glucose tolerance testing, meal challenge, A1C elevation, or decreased insulin sensitivity (29–31,33–35). In one study, the dose of ibutamoren was reduced from 25 to 10 mg daily as FBG increased to >140 mg/dL in five patients (6%) and was discontinued in three because of ongoing hyperglycemia (34).

To date, given the limited data on the effectiveness and safety of these products, the FDA has approved no SARMs or GHSs for clinical use (7,27,30). Despite the FDA's position, SARMs and GHSs, including those lacking any human investigations or dose recommendations, are widely used in fitness centers (6). Both SARMs used by the patient in this case belong in this latter category. Only animal studies have shown their anabolic effects, with a decrease in fat mass (15,36,37). Moreover, andarine seems to decrease gonadotropins in

rats, while RAD140 lowers lipids (triglycerides and LDL and HDL cholesterol) in cynomolgous monkeys.

Could This Patient's Severe Hyperglycemia Have Been Related to His Use of PEDs?

It must be highlighted that our patient had diabetogenic potential, which may have facilitated the metabolic crisis described herein. This potential for diabetes development was related to family history (both parents had obesity and his mother had type 2 diabetes), and a health check-up 3 years earlier showed metabolic syndrome (class I obesity, IFG, mixed dyslipidemia, hyperuricemia, and liver steatosis).

In the year after our patient ceased taking PEDs, his glucose values decreased to IFG levels, and his A1C normalized. His diet improved and he resumed high-volume physical activity, and only minor hypoglycemic therapy was used. His HOMA-IR decreased slightly from 4.18 to 3.6, a value that is above the proposed limit of 2.0 for healthy people without liver steatosis (38). Likewise, his dyslipidemia and hepatopathy did not resolve completely within this year.

An important key in this case is the IR condition, predominantly hepatic, as suggested by IFG, nonalcoholic fatty liver disease (NAFLD), mixed dyslipidemia, and HOMA-IR values. Individuals with NAFLD also show significant adipose tissue and muscle IR and are at high risk of type 2 diabetes (39). Adipose and muscle IR were not tested because of our clinical practice setting. We think that this patient was probably able to counterbalance this unfavorable metabolic condition for years with his intense physical activity program, which had a positive effect on insulin sensitivity, especially in his muscles (40).

Despite this dysmetabolic status, we believe that the hyperglycemic crisis was triggered by the addition of PEDs. The time between starting PEDs and diabetes manifestation (a 2- to 3-month delay) and the short time required to recover his initial status after quitting PEDs strongly suggest a causal relationship. This explanation is in line with one article reporting that hyperglycemia developed after 3.5 months of bovine GH and anabolic steroid abuse (3). To the best of our knowledge, no case of SARM- and GHS-induced diabetes has been reported yet.

Some indirect and putative explanations can be proposed for this clinical picture. The most important player seems to be ibutamoren. The dosing of ibutamoren in our patient corresponds to that used in clinical trials. As described above, ibutamoren may induce hyperglycemia and IR through a putative increase in GH with a direct effect on gluconeogenesis and insulin signaling (22). Ibutamoren could also directly alter insulin secretion through GHS/ghrelin receptors localized in the pancreas (41), as does ghrelin (42). Therefore, we tend to relate hyperglycemia to ibutamoren, as SARMs seem to be glucose neutral (17,21).

Another putative and more complex mechanism seems to be increased lipolysis. Some evidence led us to believe that ibutamoren and SARMs played a role. Although ibutamoren was not confirmed to induce loss of fat mass in clinical trials, it increases GH, which is well known for its lipolytic properties. Of note, for certain SARMs (enobosarm), lipolytic and antilipogenic effects were described in vitro, similar to the effects of testosterone (43), together with a reducing effect on fat mass in rats (andarine) and humans (enobosarm) (17,37).

Thus, we hypothesize that the additive effect of all three PEDs led to lipolysis with the following harmful metabolic effects: *1*) high levels of free fatty acids (FFAs) decreased glucose utilization because FFAs compete with glucose as an energy substrate for oxidation in muscle (22), stimulate gluconeogenesis in the liver, and have lipotoxic effects on β-cells (23) and *2*) increased lipolysis, together with IR and relative insulin deficiency, could have participated in accelerated triglyceride synthesis by the liver and led to very high triglyceride levels (44). We can indirectly infer that major lipolysis had taken place based on changes in body weight and composition. General catabolism and dehydration could partly explain the initial weight loss, whereas after care and discontinuation of PEDs, fat mass increased (2.8 vs. only 0.3 kg of LBM) from week 1 to week 10. This rebound, despite following a healthful diet and resuming intense physical activity, suggests high fat mass catabolism during PED use.

Finally, as a result of all of these processes, rising glucose levels might have further hampered insulin secretion (45) and sensitivity (46) via direct glucotoxic effects. Therefore, a vicious cycle of severe IR and altered insulin secretion developed. This cycle was interrupted by therapeutic intervention. The patient returned to his former metabolic setting corresponding to a metabolic syndrome.

Other Laboratory Findings

In accordance with previous reports (17,21), our data suggest a suppressive effect of SARMs on hepatic SHBG

production, resulting in low total testosterone and estradiol levels, although free testosterone and gonadotropins remained normal. After discontinuing the use of PEDs, SHBG, total testosterone, and estradiol returned to normal values.

Clinical Pearls

- Among recreational athletes, many PEDs are used despite the lack of clinical and safety data.
- PEDs are often used in combinations, which may potentiate their side effects.
- Clinicians should be aware of adverse events and possible health consequences of PED use. Our case suggests another adverse event: severe hyperglycemia with dyslipidemia without ketosis.

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DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

R.So. collected data, wrote the manuscript, contributed to discussion, and reviewed/edited the manuscript. R.Su. researched data and reviewed/edited the manuscript. J.-L.A. contributed to discussion and reviewed/edited the manuscript. R.So. is the guarantor of this work and, as such, had full access to all the data in the case presentation and literature review and takes responsibility for the integrity of the information presented.

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