Case Report

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Remission of type 2 diabetes and pleiotropic effects of long-term testosterone treatment for "late-onset" hypogonadism: A case report

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Abstract

For obese type 2 diabetes patients, weight reduction is one of the most important measures but fails in most cases. Testosterone deficiency can be the reason for such failure. This case presents a 57-year-old man who was referred to a urologist due to benign prostatic hyperplasia and erectile dysfunction. He had type 2 diabetes, was overweight, and had hypertension and dyslipidemia. The blood test revealed testosterone deficiency. Under testosterone therapy, the patient lost 10 kg; cardiometabolic parameters returned to normal and lower urinary tract symptoms disappeared; complete remission of diabetes was recorded. Overweight and obese patients with type 2 diabetes should be tested for hypogonadism and testosterone therapy, if indicated, be considered. These patients can considerably benefit from testosterone therapy in terms of sustainable weight loss and a clinically significant reduction of cardiometabolic risk factors including complete remission of diabetes.

Keywords

Testosterone therapy, type 2 diabetes, "late-onset" hypogonadism, obesity, cardiometabolic risk factors

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Introduction

Obesity in patients with type 2 diabetes mellitus (T2DM) is linked to multiple cardiometabolic risk factors. In addition to classical risk factors such as high low-density lipoprotein (LDL) cholesterol, hypertension, and elevated HbA_{1c}, risk factors emerging from abdominal obesity are added, such as insulin resistance and adipose tissue–associated inflammation. "Diabesity," a term being used for obesity-associated diabetes, can substantially decrease life expectancy, diminish quality of life, and increase healthcare costs.[1,2] In individuals with low testosterone, cardiometabolic risk escalates with disease duration, in particular for patients who already have a history of coronary artery disease.

For overweight and obese patients with T2DM, weight reduction has a high priority. Bariatric surgery can provide substantial and sustained effects on weight loss and obesity-attributable comorbidities including remission of diabetes but bears the risk of complications, reoperation, and death.[3,4] Moreover, bariatric patients need long-term post-surgical surveillance for nutritional deficits. Most desirable and worthwhile is a weight reduction achieved through diet and exercise in combination with sustainable lifestyle changes. However, these attempts fail in most cases in the long run. For male patients, a possible reason for such failure is an undiagnosed and untreated hypogonadism. As testosterone plays a crucial role in the biochemical processes of fat loss, muscle growth, and physical activity, sustainable weight loss is hardly feasible for patients with testosterone deficiency. Testosterone levels correlate negatively with both body mass index (BMI) and waist circumference, and thus

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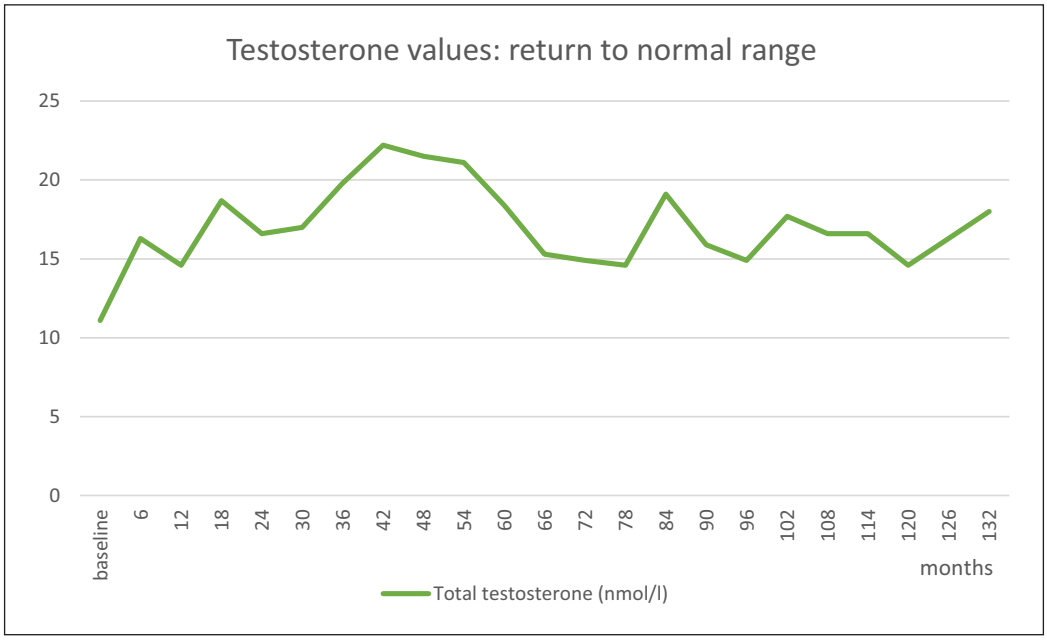

Figure 1. Testosterone values measured prior to each injection (trough values) returned to the normal range right after the first treatment and remained at that level onward.

the prevalence of hypogonadism increases with higher BMI and waist circumference. According to recent studies, more than half of obese men are found to be hypogonadal with up to 79% of all excessively obese men (BMI $\geqslant$ 40 kg/m^2).[5,6] Consequently, the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) and The Endocrine Society recommend that men with obesity, increased waist circumference, and/or diabetes should be assessed for hypogonadism and, in case of low testosterone and symptoms of androgen deficiency, be considered for therapy with testosterone.[7,8]

Case

This case presents a 57-year-old man with a history of a myocardial infarction 1.5 years ago. He was referred to a urologist when he developed benign prostatic hyperplasia (BPH) and, in addition, complained about erectile dysfunction (ED), fatigue, and low physical fitness. At the time of referral, the patient had been diagnosed with T2DM since 4 years and was under metformin medication (1000 mg twice daily) since 2 years. His further medication consisted of simvastatin 40 mg once daily, acetylsalicylic acid 100 mg once daily, and ramipril 5 mg twice daily. A BMI of 28.4 kg/m^2 and a waist circumference of 102 cm indicated overweight and abdominal obesity. Diabetes control was insufficient (HbA_{1c}: 7.2%; fasting blood glucose: 6.6 mmol/L) and increased insulin resistance (HOMA-IR: 8.5) and dyslipidemia (total cholesterol: 7.4 mmol/L; LDL cholesterol: 4.9 mmol/L; high-density lipoprotein (HDL) cholesterol: 0.9 mmol/L; LDL/HDL ratio: 5.4; triglycerides: 3.0 mmol/L) were noted. His systolic blood pressure was 176 and diastolic blood pressure was 118 mmHg.

The blood test revealed a total testosterone level of 11.1 nmol/L which was slightly below the normal range of 12 nmol/L as defined by the European Association of Urology,[9] and thus testosterone therapy (TTh) was started with depot injections of testosterone undecanoate (intramuscular (i.m.) injections at 3-month intervals after an initial 6-week interval). Prior to each injection, the patient was routinely examined throughout the observation period of meanwhile 11 years and 9 months. Testosterone values were determined on two separate occasions before commencing TTh and then prior to each injection representing trough values. Right after the first injection, testosterone returned to the normal range and remained at that level throughout the observation time (Figure 1).

During the first 4 years of TTh, the patient constantly lost weight (–10 kg) and waist circumference was reduced by 8 cm, resulting in a BMI of 25 kg/m^2 (Figure 2(a) and (b)). The weight loss was sustained throughout the observation time, that is, the patient did not regain weight during the following years.

Under TTh blood glucose level and lipid profile normalized progressively, HbA_{1c} remained below 6.5% from month 21 onward and below 5.7% from month 36 onward; fasting blood glucose decreased to 6.0 mmol/L after 3 months, to below 5.7 mmol/L after 12 months, and then remained permanently below this value; insulin resistance constantly improved (HOMA-IR: 3.9 at month 24; Figure 3); serum

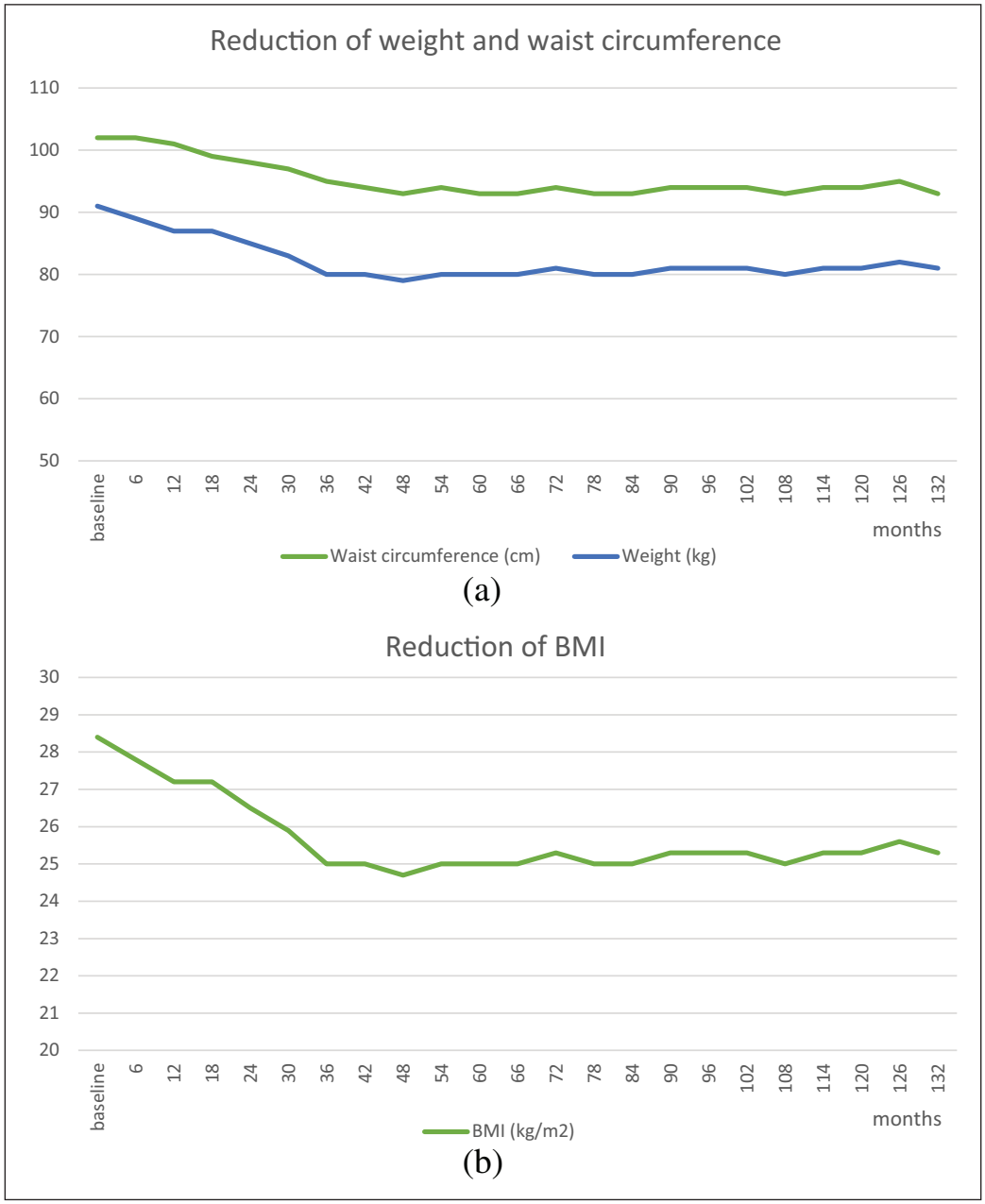

Figure 2. (a) Significant overweight at baseline was reduced to nearly normal weight within the first 4 years of TTh and weight reduction then maintained onward; (b) a BMI of originally 28.4 kg/m^2 was reduced to 25 kg/m^2 within the first 4 years of TTh.

lipid levels dropped back to normal (LDL/HDL ratio <3 and triglycerides $\leqslant 2.5$ mmol/L from month 30 onward; Figure 4(a) and (b)). A high blood pressure of originally 176/118 mmHg despite prescription of anti-hypertensive drugs decreased to 137/84 mmHg at month 30 (Figure 5). This improvement allowed the reduction of metformin 1000 mg from twice to once daily at month 10 and total cessation of metformin medication at month 30. The values further improved even after metformin had been discontinued. As a result of improved hypertension, ramipril 5 mg could be reduced from twice to once daily at month 25, and simvastatin medication was reduced from 40 mg once daily to 20 mg once daily at month 38. At the beginning of year 6, both ramipril and, based on the sustained improvement in lipid profile, simvastatin were stopped completely upon decision by the patient's family physician.

Furthermore, the lower urinary tract symptoms (LUTS) significantly improved: residual bladder volume of originally 55 mL dropped to 10 mL (despite an increase of prostate volume from 28 to 34 mL due to benign BPH), and the

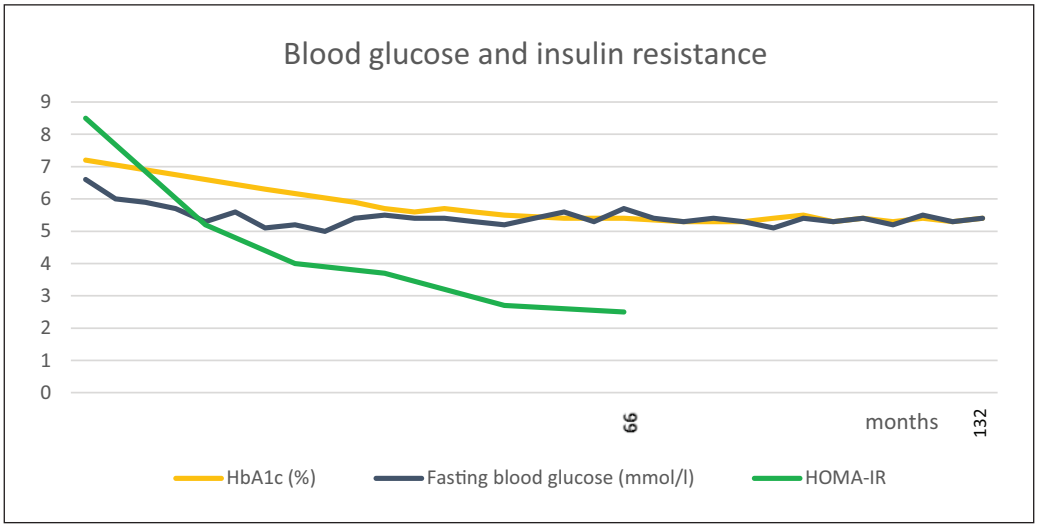

Figure 3. HbA_{1c} decreased from 7.2% (baseline) to below 6.5% from month 21 onward; fasting blood glucose decreased from 6.6 to 6.0 mmol/L after month 3 and remained below this value onward; HOMA-IR decreased from 8.5 to 2.5 at month 66 (last measurement).

International Prostate Symptom Score (IPSS) decreased from 8 (moderate symptoms) to 2 (mild symptoms). The physical, sexual, and mental well-being was evaluated as patient-reported outcome (PRO) using the Aging Males' Symptom Score (AMS).[10] The total score of 65 (severe symptoms) at the time of referral dropped below 20 (no symptoms) after 1 year of TTh and remained constant below 20 during the following years.

Discussion/conclusion

In Germany, diabetes patients have the opportunity and are advised to attend free-of-charge educational courses regarding nutrition and exercise. Obviously, this has had a poor result in our case which is not uncommon. The hypogonadal, diabetic patient presented here reduced his overweight to a healthy weight during the first 4 years of TTh. At least in part mediated by this sustained weight loss, the cardiometabolic and LUTS parameters returned to the normal range. In view of the patient's history of a myocardial infarction, this reduction of cardiometabolic risk factors is likely to preserve quality of life and maintain a more healthy life in general.

Sustainable weight loss as a sine qua non for such improvements is a well-known effect of long-term TTh in hypogonadal men. A number of studies including long-term studies with observation periods of up to 8 years provided impressive evidence of sustainable reduction of weight and waist size with simultaneous normalization of metabolic parameters.[11,12] The restored physiological testosterone levels obviously create a basis to regain a biochemical equilibrium that helps reduce body fat, increase lean muscle mass, and aid in weight management. Increases in energy and vitality help facilitate physical activity which may further improve insulin sensitivity of the muscle and liver and support weight loss.

Unfortunately, it was not possible to measure body composition in our setting. However, TTh invariably results in an increase in lean body mass.[13] This effect is approximately threefold greater with i.m. injections compared to transdermal gels.[14] Relative muscle mass is inversely associated with insulin resistance.[15] Hence, changes in body composition may have strongly contributed to the effects observed in the present case. This was impressively confirmed in a randomized, double-blind, placebo-controlled study by Dhindsa et al.[16] in hypogonadal men with T2DM where lean body mass increased with a parallel reduction in insulin resistance within as little as 24 weeks.

Remission of T2DM is rarely achieved or recorded.[2,4,17] Long-term analysis of T2DM patients with low testosterone ("late-onset" hypogonadism) under TTh is still not a widespread practice. However, from our ongoing registry database analysis, we were already able to report a case where all critical laboratory values related to T2DM substantially improved and even normalized under TTh.[18] The strength of this actual case report is the presentation of a patient with complete remission of T2DM, demonstrated by the progressive normalization of HbA_{1c} and the achievement of normal glucose regulation from month 36 of TTh onward, now documented for 11 years. Furthermore, beneficial effects were achieved on all components of the metabolic syndrome. Remission of T2DM may result from the changes in body composition combined with weight loss and maintenance of weight loss. Since the patient's weight loss under TTh is sustained, also the remission is expected to persist. Further long-time studies are desirable and we will continue recording data aiming at further confirmation of results.

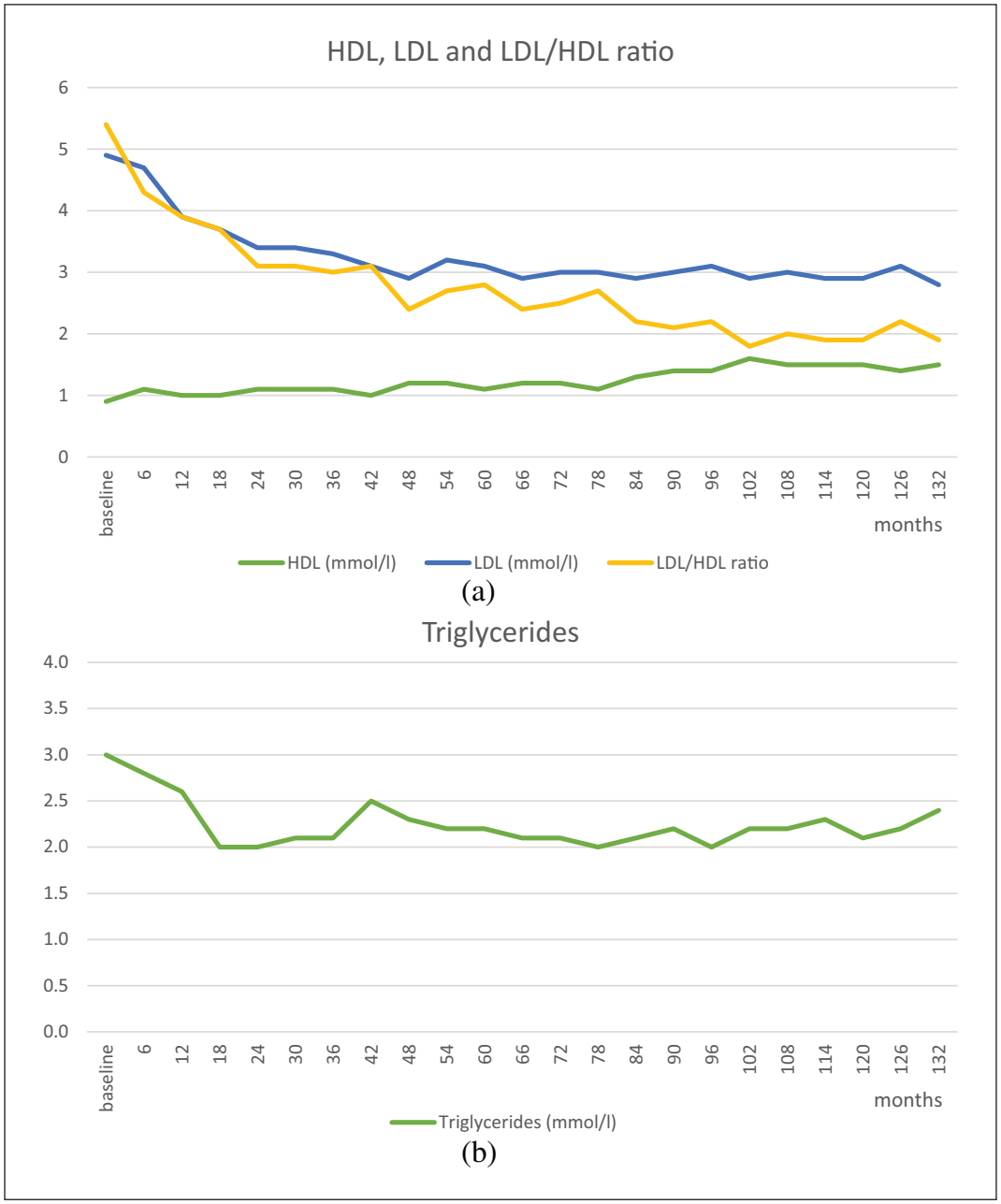

Figure 4. (a) The LDL/HDL ratio decreased from 5.4 (baseline) to below 3 from month 30 onward; (b) triglycerides decreased from 3.0 mmol/L (baseline) to below 2.5 mmol/L from month 42 onward.

The effect of TTh on quality of life is demonstrated impressively by the AMS evaluation. It has to be noted that not only did the score drop during the first year of treatment but it also remained at a low level during the following 10 years despite the patient's aging.

In their recently updated guidelines, the American Diabetes Association (ADA) has added a recommendation to measure testosterone in men with diabetes and signs and symptoms of hypogonadism.[19]

In summary, we are confident that overweight and obese patients with hypogonadism and T2DM can benefit from TTh. The benefits may be mediated by sustained weight loss and changes in body composition, resulting in a significant reduction of cardiometabolic risk factors including remission of T2DM. These improvements may lead to enhanced quality of life in patients suffering from the frequent combination of obesity, metabolic syndrome, T2DM, and cardiovascular disease together with a simultaneous reduction of healthcare

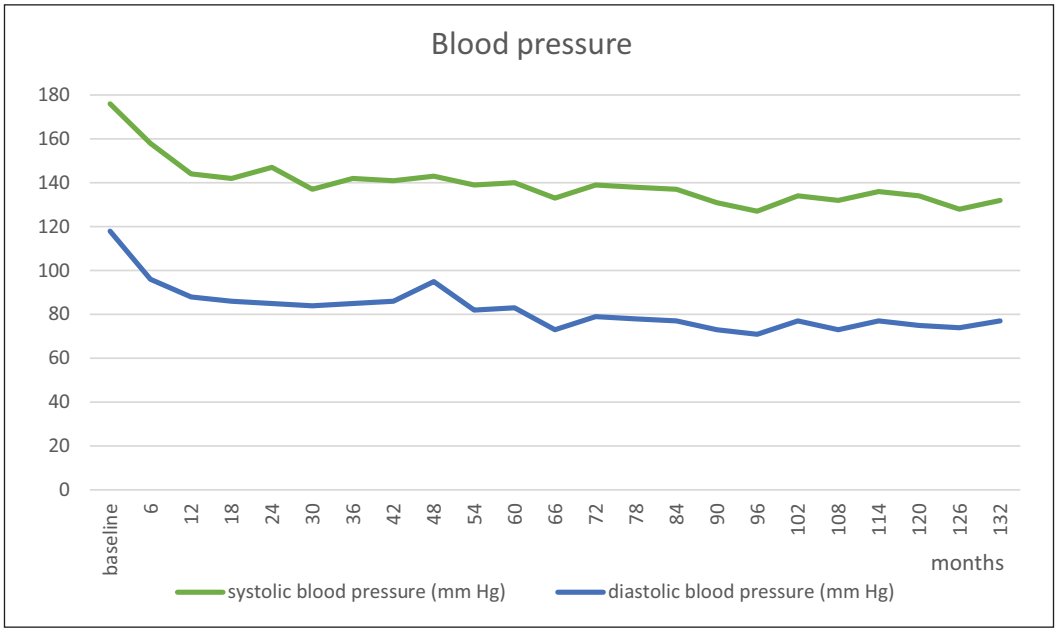

Figure 5. Blood pressure of 176/118 mmHg at baseline normalized to 137/84 mm Hg at month 30.

costs. Controlled, randomized studies are needed for further confirmation of the findings shown in this case presentation.

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Availability of data and material

The datasets used and analyzed during this case study are available from the corresponding author on reasonable request.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: A.H. has received partial funding for a registry study and travel grants from Bayer AG; K.H. has received travel grants from Bayer AG; F.S. is a full-time employee of Bayer AG.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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Informed consent

Written informed consent was obtained from the patient for his anonymized information to be published in this article and is available on request.

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