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RESEARCH

Acute changes in haematocrit leading to polycythaemia in late-onset hypogonadism patients that receive testosterone replacement therapy: a South African study

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Background: According to the literature, parenteral testosterone replacement therapy (TRT)-induced polycythaemia is associated with cardiovascular events. No or minimal data exist for the prevalence of TRT-induced polycythaemia in late-onset hypogonadism (LOH) patients from South Africa. Polycythaemia is the side effect most frequently associated with parental TRT formulations.
Design: This was a quantitative, observational, descriptive, retrospective study.
Setting: The study setting was a private practice male clinic in Emalahleni.
Subject: An all-inclusive sampling method was used.
Outcome measures: The main outcome measure for polycythaemia was haematocrit (Hct). An Hct percentage of > 50% at month 3 (post-treatment initiation) constituted a positive diagnosis for polycythaemia. For the rise in total testosterone (TT) and Hct, the variance was used as documented between pre- and post-treatment initiation.
Results: The prevalence of polycythaemia was 34%. A statistically significant increase in both TT and Hct was observed. The Cohen's *d* effect size was 0.68 and 0.73, respectively, for TT and Hct.
Conclusion: Depot-testosterone undecanoate parenteral formulation induces polycythaemia in LOH patients, where the rise in TT demonstrates the effectiveness of therapy.

Keywords: depot-testosterone haematocrit, late-onset hypogonadism, polycythaemia, testosterone replacement therapy, undecanoate

Introduction

Hypogonadism is a syndrome related to androgen deficiency. This can be sub-classified into four separate syndromes to narrow down the specific aetiology: primary hypogonadism, secondary hypogonadism, androgen insensitivity/resistance hypogonadism and late-onset hypogonadism (LOH). The inability of the testes to produce androgens even if they are sufficiently stimulated is known as primary hypogonadism. A disruption of the neuroendocrine system results in secondary hypogonadism and androgen insensitivity/resistance hypogonadism is due to the inability of the androgens to elicit a full response on the androgen receptor. LOH is defined as the disruption of stimulus between the neuroendocrine system and the testes that under normal circumstances will lead to androgen production and secretion by the testes. LOH men had normal development through puberty and therefore developed accordingly in sexual characteristics.[1]

The ageing population is expected to increase,[2] yet ageing does not always parallel optimum health. Low levels of total testosterone (TT) in association with sexual symptoms that comprise low libido, erectile dysfunction and a poor morning erection are the clinical and biochemical symptoms that manifest the most in patients prior to a positive LOH diagnosis.[3,4] These symptoms are not only the first clinical symptoms to manifest but, according to Liu *et al*., may be used in combination with low levels of testosterone to diagnose LOH.[5]

TRT is the cornerstone of treatment for LOH and other androgen deficiency syndromes.[6] Benefits of treatment include a rise in the TT level, where a TT level above 12 nmol/l is considered physiologically normal.[2] Additional clinically beneficial effects related to TRT include the increase of bone mineral density, and favourable effects on muscle mass, sexual parameters, strength and mood.[2,7] Another secondary advantage associated with TRT is the improvement of the inverse relationship between low testosterone levels and metabolic syndrome, which includes clinical conditions such as central obesity, hypertension and unsatisfactory lipid profiles that are associated with a greater risk for cardiovascular disease and atherosclerosis.[2] Furthermore TRT significantly improves glycaemic control of the type 2 diabetes mellitus patient and it is recommended that all these male patients are also screened for hypogonadism.[4] In order to maximise patient adherence and cooperation, different formulations exist that should be prescribed in accordance with patient blood levels and ability to comply with dose frequency and route.[8]

Various types of TRTs are available, which include oral formulations, implantable pellets, parenteral formulations, buccal tablets, transdermal patches and topical gels.[9] Side effects most frequently associated with TRT formulations are: less than optimal taste for oral tablets, person-to-person transfer due to close contact of individuals shortly after application of the topical gels, and gum pain is frequently reported with the use of buccal tablets.[8] Furthermore, transdermal patches cause

skin rash in some patients, where extrusion of the implantable pellet has also been documented in a number of treated patients.[10] Side effects most frequently experienced related to the parenteral dosage formulations such as testosterone cypionate, testosterone propionate or testosterone enanthate are supra-physiological testosterone levels shortly after the dose, followed by sub-therapeutic levels prior to the next dose.[9,11] This phenomenon can partly be explained by molecular esterification. Esterification processes make molecules more lipid soluble, which, in turn, enables the molecule to be more readily released from circulation.[12] This might benefit the molecules' pharmacokinetic profile, as in the case of the depot-testosterone undecanoate formulation.[11] The pharmacokinetic benefits of the depot-testosterone undecanoate formulation include a more favourable spread of TT levels around the median physiological testosterone value, with a beneficial clinical implication of less frequent dosing than older generations of testosterone. However, an increase in the number of erythrocytes above the physiological normal levels, also known as erythrocytosis or polycythaemia, is the risk most frequently encountered with parenteral TRT,[13] even though the exact mechanism of action still needs to be explained.[14] Androgen replacement therapy induced polycythaemia originates via the bone marrow haematopoiesis pathway, as an alternative to the oxygen-erythropoietin cascade.[15]

Despite polycythaemia-induced cardiovascular complications, the depot-testosterone undecanoate parenteral formulation remains the only registered TRT in South Africa to treat LOH.[16,17] Subsequently, this study has set out to evaluate, in retrospect, the prevalence of polycythaemia among diagnosed LOH patients who have received depot-testosterone undecanoate TRT and the possible clinical significance thereof.

Method

Setting

The study took place in a private practice located in Mpumalanga, ranging from Emalahleni (formerly known as Witbank), Groblersdal and Nelspruit, South Africa. By undertaking a study that covered all these towns, a large study population from different geographical areas was ensured. The study was approved by the Ethics Committee of North-West University (NWU-00082-17-S1).

Subject selection

Inclusion criteria

Data were subject to the following criteria. Only data of confirmed LOH cases were included in the current study, where depot-testosterone undecanoate was initiated as normal standard practice according to the specialist prescription.

Exclusion criteria

Data of patients with signs and symptoms of conditions such as severe sleep apnoea, male breast cancer or an Hct > 50% at the time of diagnosis, and prostate specific antigen >4 ng/ml at the time of diagnosis were excluded from the study, as alternative treatment plans had to be applied by the treating practitioner.

Research procedure

This study investigated retrospective data of diagnosed LOH men who followed the European Association of Urology treatment regimen for depot-testosterone undecanoate for at least a three-month period. The observation was done in retrospect, where treatment was initiated on day 1, a booster at six weeks after the first injection, and then after 12 weeks.[1,9]

The data required to execute the study were obtained from the clinical data manager of the specified private practice. These included re-identified patient data of laboratory TT levels and Hct values as recorded by the clinical data capturer at the time of diagnosis (month 0), and three months post-treatment. A positive diagnosis for polycythaemia was made once an Hct percentage of > 50% was obtained from the laboratory. The raw data were sent to Statistical Consultation Services of North-West University for data analyses.

Data analysis

The Statistical Analysis System®, SAS 9.3® (SAS Institute Inc., Cary, NC, USA) was used to analyse the data. Categorical variables were reported as frequencies and percentages. Continuous variables were reported as mean ± SD (normally distributed data) or median (25th, 75th) percentiles (skewed data). Histograms and Q-Q plots were used to evaluate the distributions. Possible outlying values were identified by means of box-and-whiskers plots, with *z*-score values larger than the absolute value of three. The dependent t-test was used to compare the change between the two time points. Cohen's *d*-value was used to determine the practical significance of the results (with $d \geq 0.8$ defined as a large effect with practical significance).

Results

The cohort of LOH patients was observed retrospectively for a three-month study period. Polycythaemia was observed in 34% of participants.

The mean Hct rose from 45.62% (standard deviation [SD] 4.79) to 49.11% (SD 3.98). The change in mean Hct over the study period was 3.49% (SD 4.46). The rise in Hct was statistically significant, p-value < 0.001. The effect size was 0.73, suggestive of a large impact.

At the beginning of the study, the participants' mean TT was 8.18 nmol/l (SD 3.71), and at the end of the three-month period it was 12.39 nmol/l (SD 6.18). The mean increase of TT over the study period was 4.21 nmol/l (SD 6.47). The increase in TT had a statistically significant p-value < 0.001. Cohen's *d*-value of 0.68 suggests a large practically significant change over the two time points. A negative association between Hct and TT was noted after the study period.

Discussion

Depot-testosterone undecanoate-induced polycythaemia occurred in 34% of study participants, with an overall study period recorded mean Hct of 49%. This mean Hct value was below the upper level stated as pathognomonic for polycythaemia (Hct > 50%).[1] The rise in TT of the study participants ($n = 49$) after initiated treatment proved to be practically significant, as TT levels increased to within the normal physiological TT level of 12 nmol/l.[2] The observed change in Hct and TT values was statistically and practically noteworthy, indicative of the importance to evaluate benefits and risks related to patient care.

Polycythaemia—the increase of erythrocytes leading to higher levels of blood viscosity—is a known risk when a patient receives TRT.[1,2] Furthermore, it is well documented that polycythaemia is a dose-dependent side effect of TRT and that both dose and delivery system affect the magnitude of the Hct increase.[3,14,15,18] As observed in this study, a higher

polycythaemia prevalence is noted in some study participants, as opposed to no cases of polycythaemia recorded in studies done by Conaglen *et al*. and Yassin and Haffejee.[9,11] A possible reason for the difference noted in polycythaemia prevalence between studies is the studied population of hypogonadal men. Some authors reported Hct values that consisted of men who had previous encounters with TRT, where others used a mixed-patient population that comprised men with primary, secondary and late-onset hypogonadism.[8,19] This study, however, used only treatment-naive LOH patients. Furthermore, over- or under-reporting of polycythaemia might occur due to mean Hct values and standard deviations that mask individual results that are over the upper Hct limit. The individual masking effect was explained by Haider *et al*., where the mean Hct of 122 LOH male patients at month 3 of initiated therapy revealed no cases of polycythaemia in relation to a 5% prevalence of polycythaemia after evaluating patients individually post-treatment (at month 3).[20] The latter might be resolved by grouping patients according to their own individualised Hct values.[20] Finally, a polycythaemia-induced Hct cut-off value still eludes prescribers and patients as discussions still exist as to what the peak cut-off Hct percentage should be. Haematocrit values ranging from 50% to 54% were chosen by most authors.[1,14] This study used an Hct percentage of > 50% as pathognomonic for polycythaemia, which is in line with the European Association of Urology guidelines.[1]

It is important to be aware of the possible mean increase in Hct, as a steep rise above the Hct threshold level may lead to adverse effects such as strokes, myocardial infarctions or deep vein thrombosis that might well lead to a pulmonary embolism.[20,21] Despite TRT-induced erythropoiesis leading to polycythaemia, randomised control studies still cannot demonstrate the direct relationship between TRT-induced erythrocytosis and cardiovascular events.[22] In a recent review published by Hackett,[7] TRT patients presented with a 6% increase in risk for polycythaemia. However, mortality rates were lower in the TRT cohort of patients than for treatment-deprived patients, which demonstrates the beneficial effect of TRT for hypogonadism patients. There is a relationship between the mean change in Hct values of this study and other studies, which demonstrates the similarities of a mean change in Hct values between international patients and South African patients.[18] This is noteworthy for the South African population, as TRT-induced polycythaemia studies are not well defined in South Africa. Subsequently, Assi and Baz noted that any man presenting with an Hct > 52% can be diagnosed with polycythaemia[23]—further strengthening evidence that the South African male population might be comparable with international cohorts.

The statistically significant increase in testosterone experienced by the current cohort of subjects leads to TT levels close to or within normal physiological TT ranges, consistent with international guidelines.[1] The rise in TT levels depends on the baseline TT value.

Observed study limitations were the lack of hematopoietic supplementation history of patients and the fact that patients were not stratified according to possible underlying co-morbid conditions, e.g. diabetes, obesity, HIV and anaemia, as these are known conditions that have a variable effect on testosterone levels.

Conclusion

The prevalence of polycythaemia for the South African cohort of studied men was higher than that of their international counterparts. However, the mean increase of Hct was below the pathognomonic cut-off used to diagnose polycythaemia. The conclusion can therefore be made that polycythaemia is a statistically significant occurrence for some individuals, but, when put into perspective related to the broader community, polycythaemia is an isolated occurrence that should be screened for during the first few weeks to months after treatment initiation. Therefore, prescribers should strongly recommend screening for polycythaemia as per published guidelines. The rise in TT levels was sufficient to conclude that less than optimal baseline TT levels will rise to within normal physiological TT levels. To conclude, despite a greater statistically significant risk for attaining TRT-induced polycythaemia, further research needs to be conducted to determine the practical significance thereof.

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