Audit on testosterone therapy in adult males with testosterone deficiency

Josephine Bigeni, Mark Gruppetta, Matthew Zammit, Yanica Vella, Clayton Micallef, Maria Mifsud, Josanne Vassallo

Abstract

Introduction: Hypogonadism is estimated to affect between 2.1 and 12.8% of the adult male population.

Aim: The aim of this audit is to look at current practice and compare them with established guideline so as to identify areas which need improvement.

Method: A review of 235 patients suffering from hypogonadism was undertaken. Local standards of care were compare to the Endocrine Society Clinical Practice Guideline of 2010 (ESCG).

Results: Patients complained of 0, 1-4, 5-8 symptoms suggestive of hypogonadism in 17%, 67% and 16% respectively. 76.5% of the patients had repeatedly low testosterone. 20% suffered from primary hypogonadism. 77% suffered from secondary hypogonadism secondary. Karyotype was obtained in 35% and 5% of the patients suffering from primary and secondary hypogonadism respectively. Patients suffering from secondary hypogonadism had serum TSH (94%), prolactin (92%), cortisol (91%), GH levels (89%) and iron studies (43%) analysed. 77% of patients suffering from secondary hypogonadism had an MRI of the pituitary, with an abnormality reported in 53% of the patients. Prior to starting treatment 7% of the patients were assessed for prostate nodules and PSA was taken in 39% of the patients. Only 33% of the patients had bone mineral density (BMD) taken prior to starting testosterone treatment. Patients were reviewed 3-6 months (35%) and then annually (88%) after treatment was initiated.

Conclusion**:** This audit identifies the need for documentation of signs and symptoms. Testosterone levels should be repeated prior to starting treatment. It also highlights the need for karyotyping in patients with primary hypogonadism as well as the need to measure BMD and PSA before and after prescribing testosterone. Patients need review at 3-6months after initiation of testosterone supplementations.

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Key Terms

Testosterone therapy, hypogonadism, testosterone deficiency

Introduction

Testosterone deficiency is defined as sub-optimal serum testosterone levels with or without modified receptor *sensitivity* to androgens.[1] It may be further described as clinical hypogonadism (presence of signs and symptoms), or as subclinical hypogonadism (a biochemical deficiency with absence of symptom) and is estimated to affect between 2.1% and 12.8% of adult males.[2-3]

Testosterone deficiency can result from defects at different levels of the hypothalamus-pituitary-testes axis, ranging from abnormalities in the testes (primary hypogonadism), to pituitary or hypothalamic dysfunction (secondary hypogonadism).[4] Testosterone deficiency may also occur due to decreased bioavailability of the hormone (due to sex hormone binding variations) or androgen receptor alterations.[4]

Presentations includes sexual dysfunction, fatigue, mood disturbances, decline in bone mineral density (BMD) and change in body composition, erectile dysfunction, decrease morning erections and low libido being of greatest significance.[2,4-5] Due to its numerous influences on the endocrine and nervous system, testosterone deficiency is associated with a variety of co-morbidities including obesity, type 2 diabetes, hypertension, osteoporosis and cardiovascular disease. [1-2]

A definite diagnosis can be established after two morning total serum testosterone levels, with cut-off values depending on different methodology used.[2, 5-7] Treatment options for hypogonadism revolve around testosterone replacement therapy.[1-2, 6-7]

An audit was carried out with the aim of investigating patient demographists, clinical investigation, treatment and follow up of hypogonadal patients at Mater Dei Hospital. These findings were compared to the Endocrine Society Clinical Practice Guideline of 2010 (ESCG) regarding identification, diagnosis, investigations and managing patients with androgen deficiency syndromes.[7]

Aim

The aim of this audit was to review current practices in Mater Dei Hospital and compare them with established guidelines so as to identify areas which need improvement.

Patients and Methods

Sample

235 patients prescribed testosterone esters and listed on the Medical Approval Section covering entitlement for free medication from 2006 until February 2014 were included. Data analysis was carried out on 153 i.e. 65% of the cohort. In 29% of the cohort no data was available in their file while in 6% of the cohort the file could not be accessed. Case notes of adult males seen at Mater Dei Hospital who were on testosterone treatment were reviewed.

Methodology

This was an audit were medical notes and online documentation systems (Isoft® and PACS®) were used to collect data on the patients' diagnosis and management. The data collection form used was based on the ESCG.[7] Data collection was done using Microsoft Access® and then data analysis was carried out by using Microsoft Excel® using simple descriptive statistics. Analysis for concordance with ESCG recommendations was subsequently carried out.

Results

Patient demographic and symptomatology

Data analysis was carried out on 153 patients (*n*). 30% (*n*=46) of the patients were below 29 years of age, 57% (*n*=87) were between 30 and 59 years of age and 13% (*n*=20) were above 60 years of age (Figure 1).). 2 patients who suffered from hypogonadism secondary to multiple system atrophy and pituitary adenoma were over 70 years of age. The most common symptoms that the patients complained of were a decrease in spontaneous erections, reduced libido, small testes and reduced body hair (Figure 2). Patients complained of 0, 1-4, 5-8 symptoms suggestive of hypogonadism in 17% (*n*=26), 67% (*n*=102) and 16% (*n*=25) respectively (Figure 3).

***Figure 1**: Age when testosterone treatment was started.*

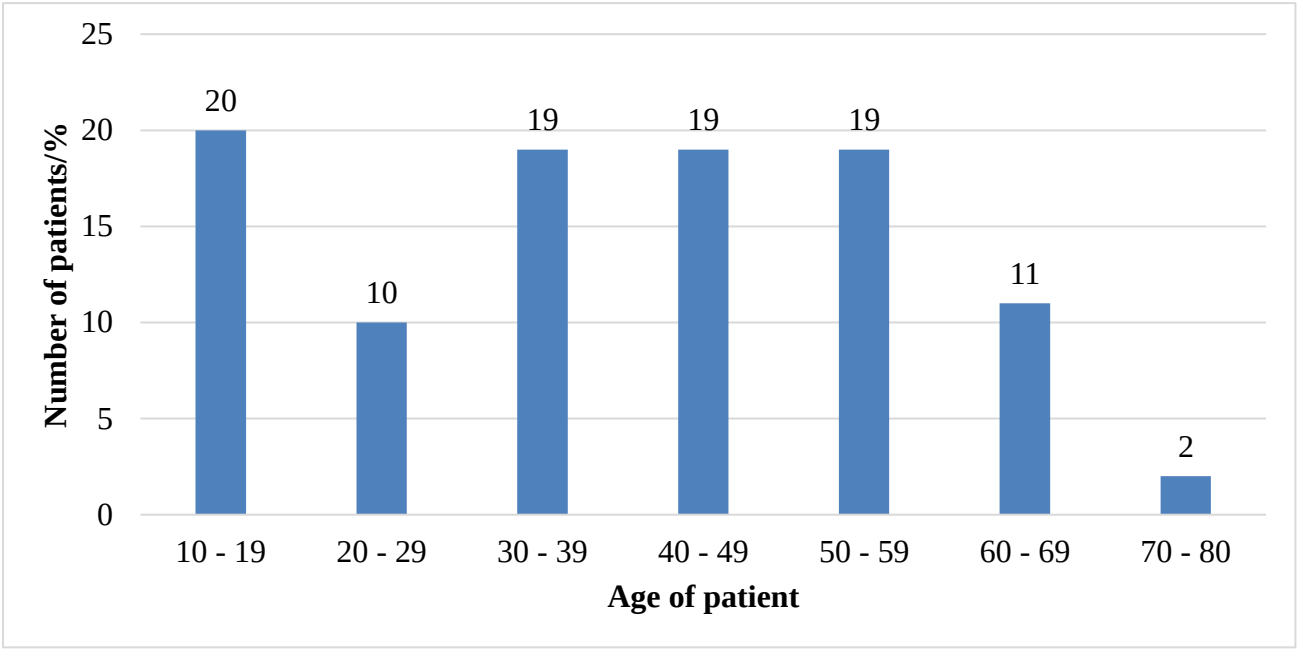


***Figure 2**: Symptoms and signs at presentation.*

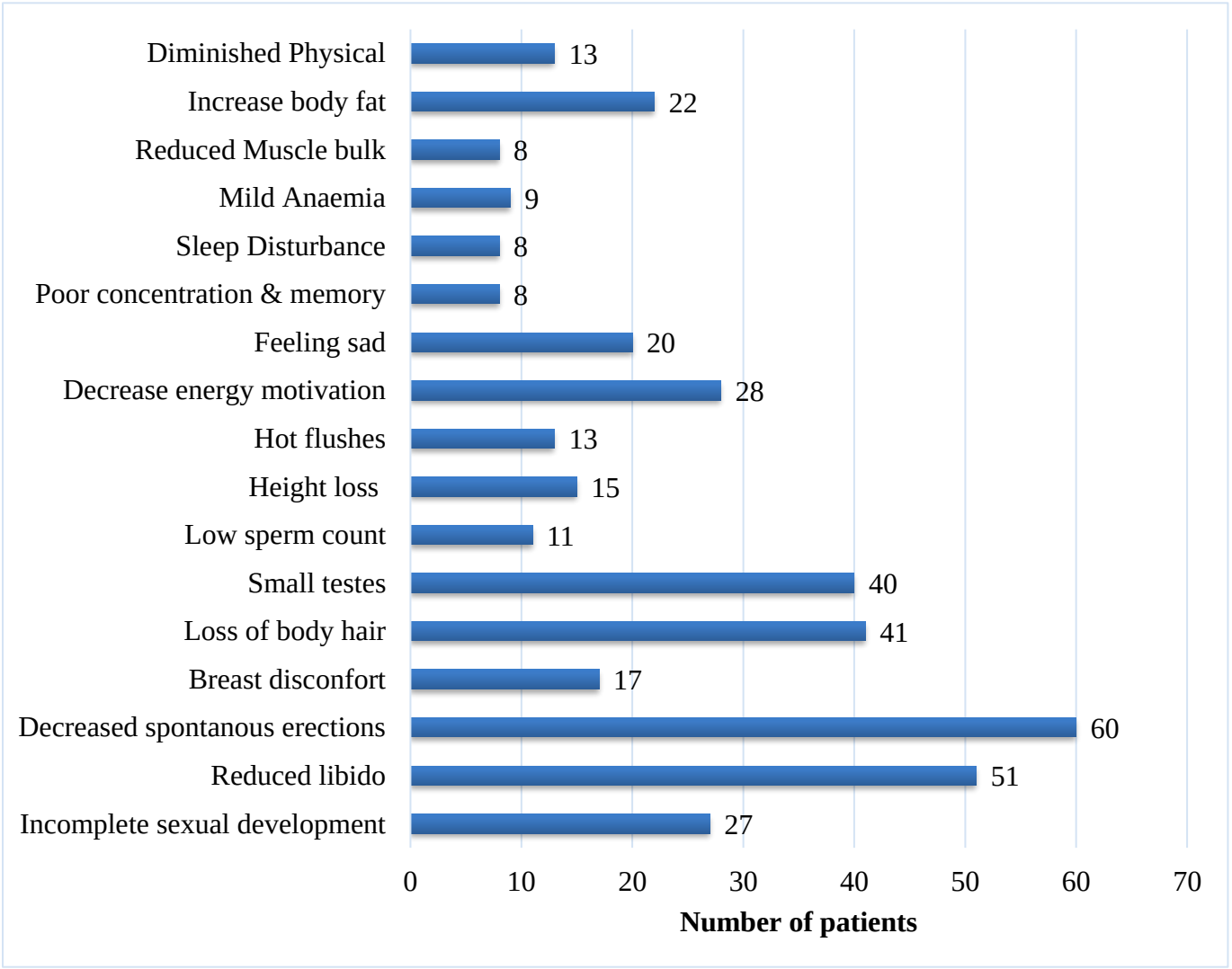
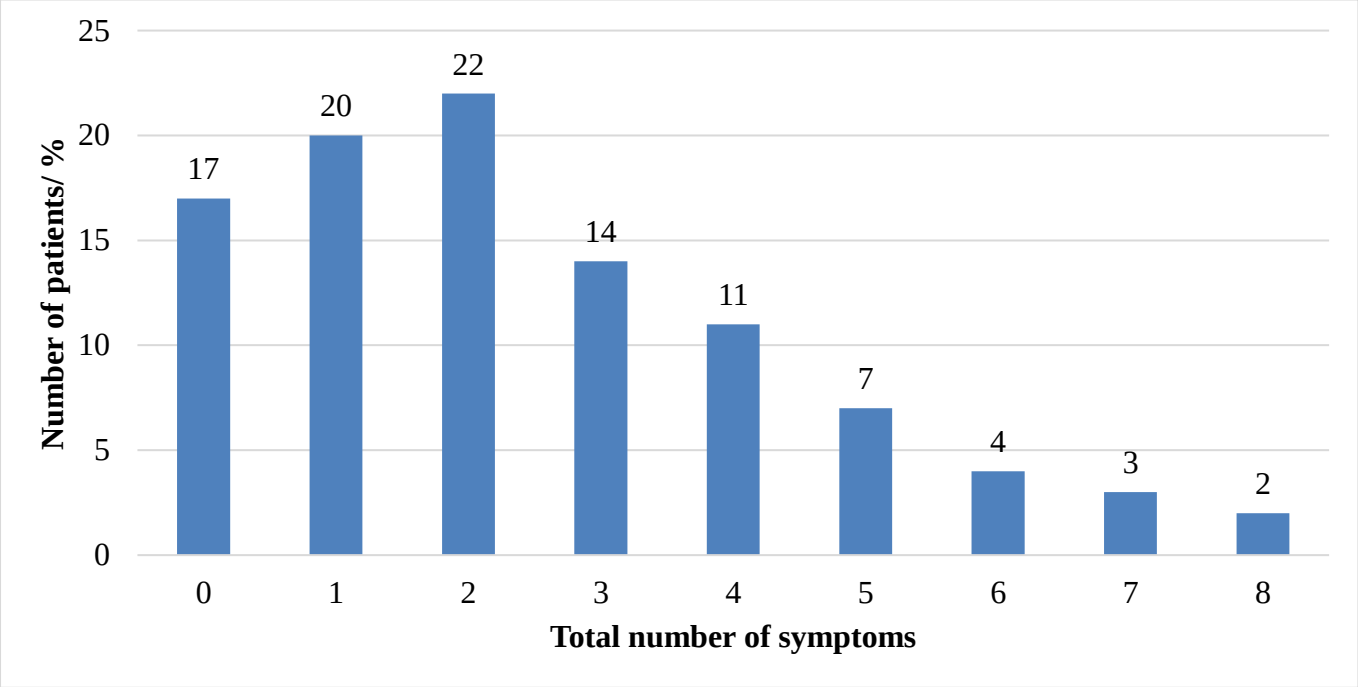


***Figure 3**: Percentage number of patients with 0 to 8 symptoms at presentation.*



Investigation

During data collection, testosterone levels were found to be below the lower limit of normal for the particular assay used. Different assays which were used over the years include enzyme–linked immunosorbent assay and chemiluminescent immunoassay. Due to the utilisation of different assays for total and/or free testosterone, different normative ranges were present over different time periods, hence graphical representations of these levels was not possible. However, 76.5% (*n*=117) of the patients had confirmation of low testosterone by repeat analysis prior to starting treatment. Sex hormone binding globulin (SHBG) was measured in 2 patients. However a number of patients (*n*=90) had conditions which could potentially affect SHBG concentration.

Karyotype was obtained in 35% (*n*=11) and 5% (*n*=6) of the patients suffering from primary and secondary hypogonadism respectively. Patients suffering from secondary hypogonadism had serum TSH (94%; *n*=110), prolactin (92%; *n*=108), cortisol (91%; *n*=107), GH (89%; *n*=104) and iron studies (43%; *n*=50) taken (Figure 4, 5). Of the 117 patients who suffered from secondary hypogonadism, 90 patients had an MRI of the pituitary, with an abnormality reported in 62 of the patients.

Diagnosis

20% (*n*=31) suffered from primary hypogonadism with Klinefelter's syndrome (5%; *n*=7) and orchidectomy (4%; *n*=6) being the most common causes (Figure 6). In 7 patients the cause was not found. 77% (*n*=117) suffered from secondary hypogonadism with pituitary adenoma (31%; *n*=47) and idiopathic hypogonadotrophic hypogonadism (14%; *n*=21) being the most common causes (Figure 7). 16 patients had no MRI done. 3% (*n*=5) of the patients could not be classified as suffering from primary or secondary hypogonadism since LH and FSH levels were not available.

Treatment and follow up

No patient had a past history of breast or prostate cancer. 78 of the patients were over 40 years old when testosterone treatment was started. PSA was tested in 42 (54%) of these patients. 23 of these patients had a PSA less than 0.6ng/ml. On the other hand, 19 of these patients had a PSA more than 0.6ng/ml with only half of these having a digital rectal examination performed.

Testosterone undecanoate and testosterone enanthate were the most commonly used testosterone esters. (Table 1)

Figure 4: *Percentage of patients with hypergonadotrophic hypogonadism with karyotyping and hormone profiles*

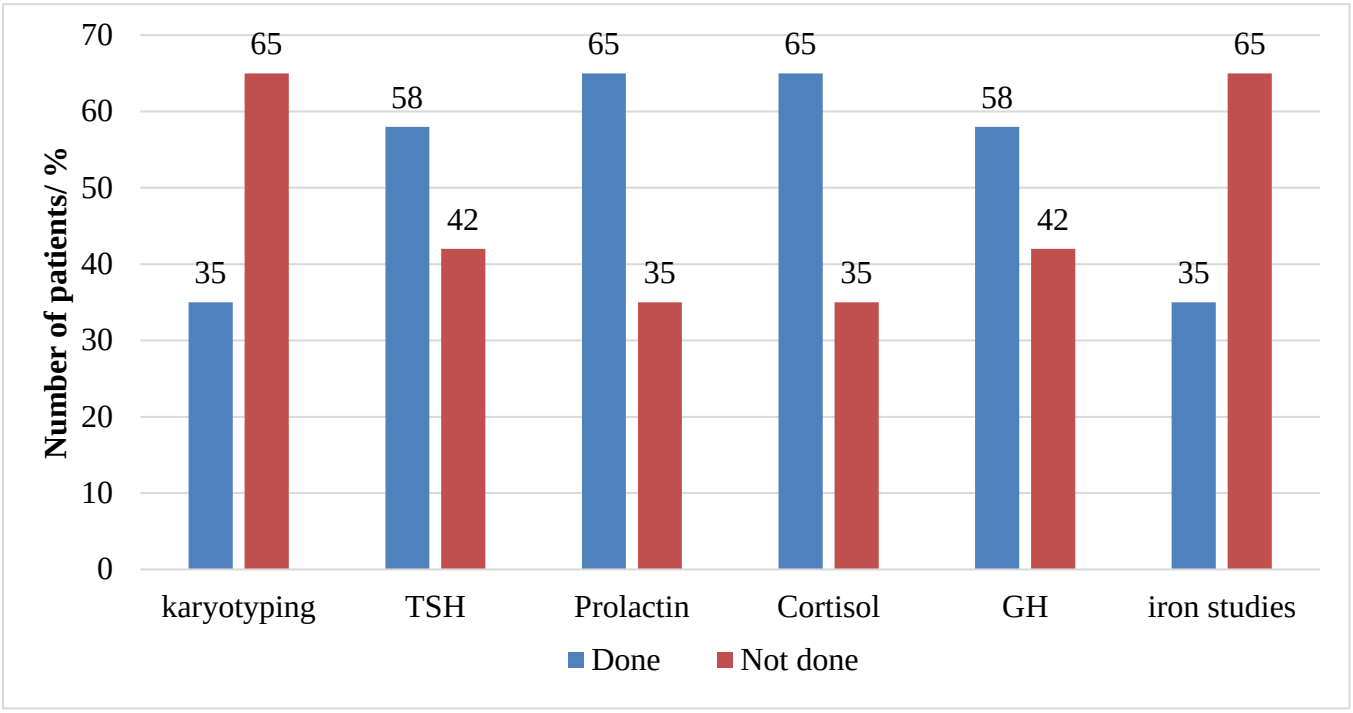


Figure 5*: Percentage of patients with hypogonadotrophic hypogonadism with karyotyping and hormone profiles*

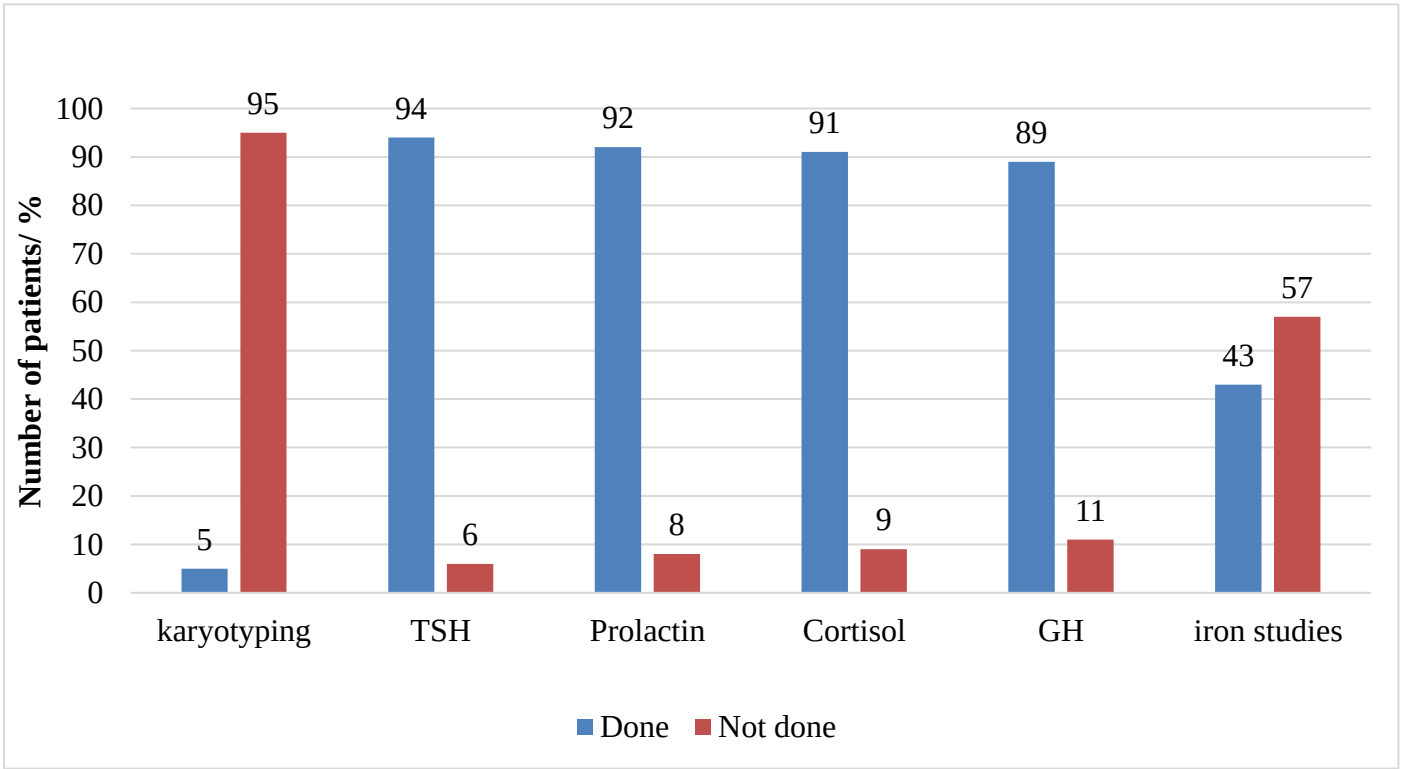


Figure 6: *Causes of primary hypogonadism (Hypergonadotrophic hypogonadism)*

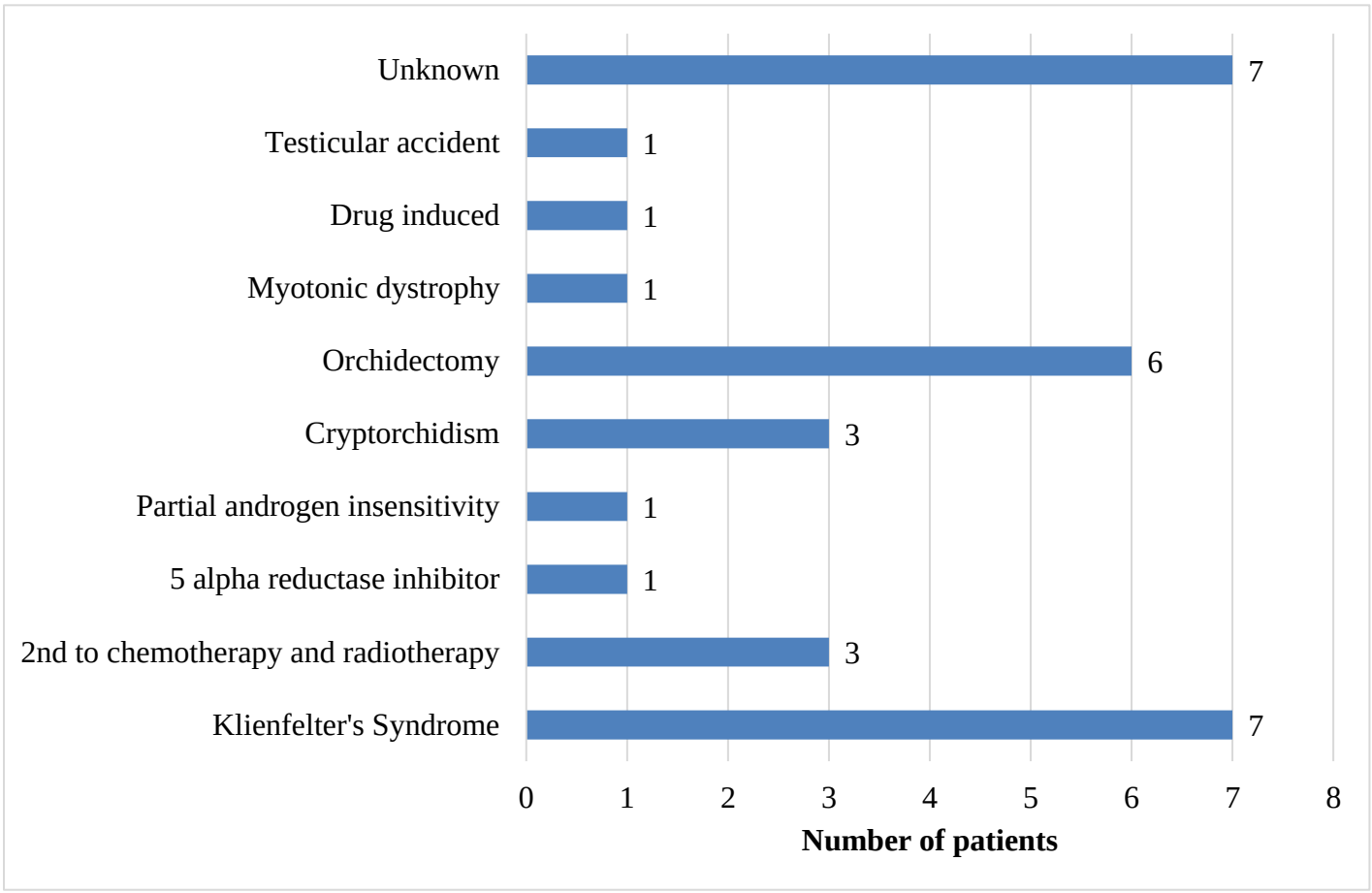


Figure 7: *Causes of secondary hypogonadism (hypogonadotropic hypogonadism)*

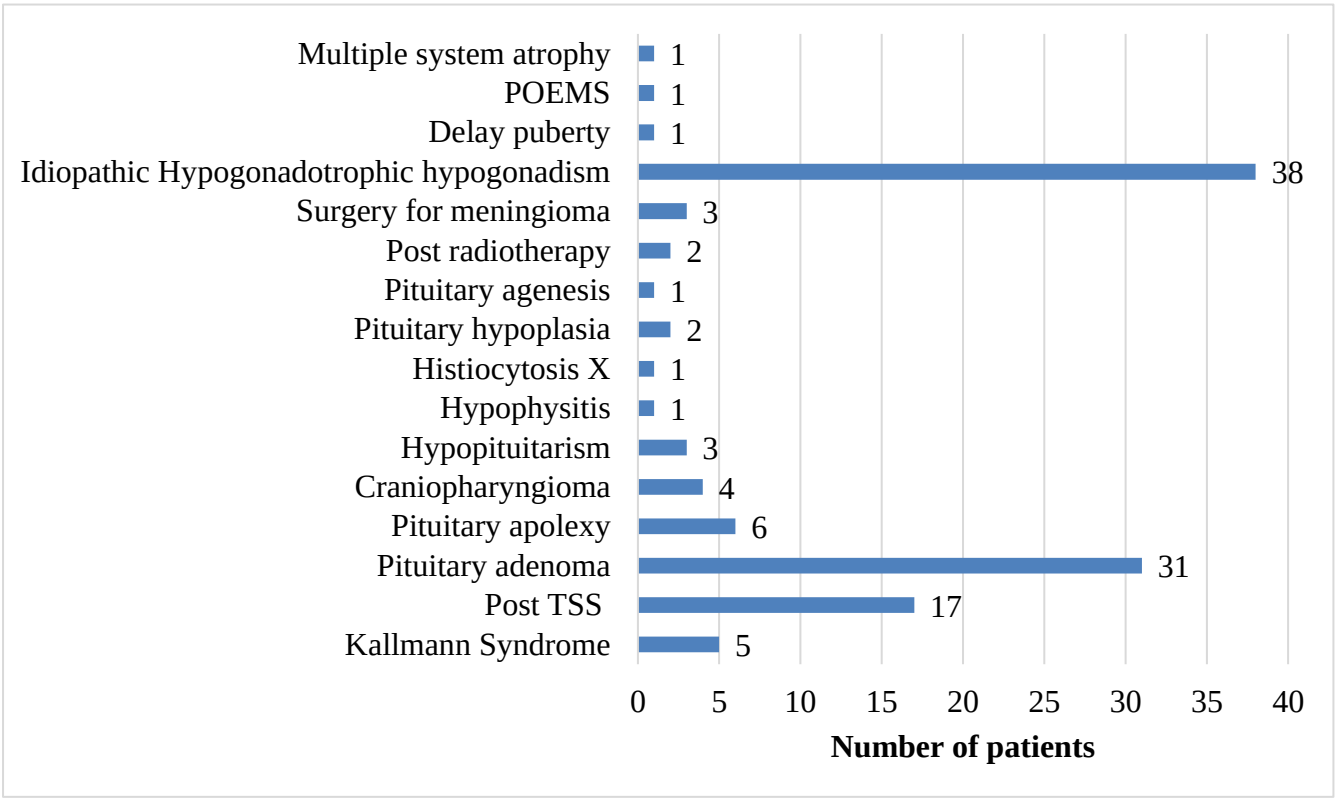


Table 1*: Type of testosterone esters used.*

Type of testosterone esters	Number of patients
Testosterone enanthate	91
Testosterone undecanoate depot	36
Testosterone undecanoate oral	4
Testosterone cypionate	1
Testosterone proprionate	1
Primotestosterone	10
Testogel	1
Not specified in notes	9
Type of testosterone esters	Number of patients
Testosterone enanthate	91
Testosterone undecanoate depot	36
Testosterone undecanoate oral	4
Testosterone cypionate	1
Testosterone proprionate	1
Primotestosterone	10
Testogel	1
Not specified in notes	9

Table 2: Bone mineral density results.

BMD at diagnosis	**Mean T score of the spine at diagnosis (+/- SD)**	**Mean T score of the spine after starting treatment (+/- SD)**	**Mean T score of the hip at diagnosis (+/- SD)**	**Mean T score of the hip after starting treatment (+/- SD)**
Normal (3pts)	-0.14 (+/- 0.61)	0.15 (+/- 0.23)	0.02 (+/-0.70)	-0.25 (+/- 1.36)
Osteopenia (9pts)	-1.59 (+/- 0.51)	-1.41 (+/- 1.18)	-1.15 (+/- 0.96)	-1.40 (+/- 0.41)
Osteoporosis (12pts)	-2.53 (+/- 1.27)	-2.71 (+/- 0.96)	-2.82 (+/- 0.57)	-2.46 (+/- 0.46)

Patients were reviewed at 3-6 months (35%; *n*=54) and then annually (88%; *n*=135) after treatment was initiated. Improvement of symptoms was documented in 50% (*n*=77) of the patients. 36 patients stated that they felt better after the treatment was started, with improved erectile function in 32 patients. 13 patients had improved libido and 19 patients had increased body hair.

80% (*n*=123) of the patients had annual haematocirt checked. All of these patient haematocrit value was less than 54% and so testosterone treatment was not discontinued for this reason.

33% (*n*=50) of the patients had BMD done prior to starting treatment with 16% (*n*=24) of these having follow- up BMD. BMD were carried out on either Norland and Hologic Bone Densitometers. BMD was assessed after starting treatment in 14% (*n*=22) of the patients. 20 patients were osteoporotic, 24 patients were osteopenic whilst 28 patients had normal BMD.

Table 2 displays patients who had BMD done at diagnosis and at follow up (16% of the patients). T score at the spine showed mild improvement in osteopenic and normal patients while slight deterioration was seen in osteoporotic patients. T score at the hip showed some deterioration in normal and osteopenic patients while there was an improvement in osteoporotic patients.

Discussion

This analysis of concordance with guidelines highlights areas which need to be improved when managing patients with hypogonadism at Mater Dei Hospital.

The gold standard methods to measure free testosterone values are liquid chromatography and mass spectrometry which are not available locally. Given this, total testosterone measurements are the best available option locally.[7-8] Free testosterone estimation would be preferred in scenarios were total testosterone levels are near the normal range and in whom altered sex hormone binding globulin (SHBG) levels are suspected (e.g. obesity, diabetes, hypothyroidism).[2,7] In our testosterone deficient patients, free and total testosterone serum levels were obtained at varying time points over the study period as a result of changes in the assays made available by the Pathology department at Mater Dei Hospital.

ESCG state that a diagnosis of hypogonadism is established after two separate measurements of morning total testosterone levels are low.[7] However results of the study show that 24% of patients diagnosed with hypogonadism had only 1 measurement. A retrospective cohort study in USA also showed lack of duplicate confirmatory testing, with only 40% of the 63,534 cohort population having 2 or more testosterone levels determinations.[9] However, all total testosterone serum testing was carried out in the morning, respecting testosterone's diurnal variation and adhering to guidelines.[7] This contrasts with a NorthShore University cohort study, were only 9% of men were tested in the early morning.[2] Barriers to guideline implementation include lack of awareness and familiarity with guidelines, patient non- compliance or environmental barriers (such as difficulty scheduling early morning testing).[2]

Karyotyping was not carried out in 65% of patients with primary hypogonadism. ESCG suggests that karyotyping is required to exclude Klinefelter syndrome (KS) in men with ''*primary testicular failure of unknown aetiology*''.[7] The incidence of KS is 0.1-2% of male neonates, being one of the commonest congenital disorders resulting in hypogonadism.[10] Due to significant variation in clinical presentation, only 10% of cases are identified before puberty and 25% up until adulthood, with the latter reported in a study using Danish patient registries.[10-11] Diagnosis should be made as early as possible in KS patients, as early treatment with testosterone helps improve their quality of life.[11] Although a combination of small testes and elevated gonadotrophins is present in the majority of KS patients, variable phenotypes, as well as mosaicism, make karyotyping essential in all patients with primary hypogonadism of unidentified aetiology.[10]

When diagnosing secondary hypogonadism; TSH, free thyroid hormone, prolactin, serum cortisol, IGF-1 and GH were assessed in the majority of patients (> 89%), whilst iron studies were documented in less than half of patients. ESCG suggest iron saturations be measured in all patients with secondary hypogonadism so as to exclude or confirm haemochromatosis.[7] The largest study on prevalence of hypogonadism in haemochormatosis reported a prevalence of hypogonadism of only 6.4%.[12] However, prevalence of hypogonadism may be decreasing due to earlier diagnosis of haemochromatosis.

Hypogonadism however still remains a significant complication and all patients with haemochromatosis should be screened for this.[12]

Testosterone enanthate followed by intramuscular testosterone undecanoate were the two commonest prescribed testosterone replacement treatment, and are recommended by ESCG.[7] However, oral forms (which include testosterone undecanoate) are associated with a high serum level variability and require multiple daily doses compared to other routes of administration.[13] This has significant implications with regards to compliance and efficacy. Intramuscular injections, subcutaneous implants, patches and gel have demonstrable better pharmacokinetics, better long term outcome and should ideally be available for patients use.[13-14]

With regards to patient follow-up, only 35% of patients were assessed at 3-6 months, whilst 88% were assessed annually, contrasting with the ESCG.[7] Canadian and other international guidelines for the management of hypogonadism also recommend these monitoring intervals.[1,4] This re-assessment should incorporate details of improvement of symptoms, possible therapeutic complications, patient adherence and biochemical monitoring (including testosterone level and PSA).[1,4] Shorter hospital outpatient appointment interval should therefore be recommended.

A limitation in our study was that we only had access to hospital files and some of the patients may have been followed up in the community. ESCG recommends assessing whether symptoms have ameliorated with treatment and if there is documentation of any adverse effects.[7] The BLAST study suggests that early sexual benefits and improvements can be effectively documented through use of the Ageing Male Symptom score.[5] A prospective study by Kovac et al. also revealed that satisfied patients reported more significant improvements in the areas of libido, concentration, mood and muscle mass higher than dissatisfied patients.[15] Adopting a standard method of symptom documentation on follow-up may help increase awareness for physicians, help identify patient complaints, and also indirectly increase treatment compliance and improve patient outcomes.

When considering complications of hypogonadism, 33% of patients had a documented baseline BMD, with only 16% of these having follow-up BMD monitoring. 14% of the total study population had BMD assessments after starting testosterone treatment. However the number of patients was very small, the bone densitometry utilised was not the same in all patients and there may have been other confounding factors making it difficult to draw up any conclusion from these figures.

In a randomized, double-blind, placebo-controlled study, Basurto et al showed how BMD in the lumbar spine significantly improved with testosterone treatment.[16] In a study done over 36 months on patients with hypogonadism and metabolic syndrome, Aversa et al showed an improvement in BMD in both lumbar spine and hip with testosterone replacement.[17] Treatment in hypogonadal men causes significant improvement in both hip and lumbar spine BMD, with significant effects on BMD reported after 6 months and an 8-10% increase over 3 years.[4-6,18] Due to the risk of decreased BMD and fractures in untreated hypogonadism, it is advisable to do bone densitometry at baseline (for future results comparison) and every 1-2 years of testosterone replacement.[1,6,8] This enables surveillance regard treatment compliance, and improvement of BMD with treatment, and subsequent appropriate dose adjustment if BMD measurements are unsatisfactory.[18] Other pathologies predisposing to osteopenia and osteoporosis should have been excluded prior to testosterone initiation.[18]

With regards to PSA testing and monitoring in patients older than 40 years, 54% of hypogonadal patients had a documented PSA at baseline prior to treatment. The association between testosterone replacement and prostate pathology is highly controversial.[19] Study by McLaren et al. revealed that continuation of testosterone replacement over a 2 year period did not raise PSA values, with minimal effect on prostate health.[20] However, a meta-analysis of randomized, placebo-controlled trials of 19 studies by Calof et al, deduced that rates of prostate cancer, significant increments in PSA levels and increases in American Urological Association/International Prostate Symptom Score scores were higher in testosterone treated men than the placebo group.[14] However, significant bias was noted in that testosterone treated patients were more likely to undergo prostate screening and biopsy than the placebo group.[14] A critical review by Jannini et al, concluded that whilst prostate cancer is androgen- dependent, no conclusive evidence for

increased prostatic cancer/ hyperplasia is available.[19] Therefore physicians should be cautious and monitor for prostate pathology.[19] The general consensus for screening includes PSA and a digital rectal examination before and during patient follow-up appointments.[1,7,21]

***Figure 8**: Algorithm in androgen deficiency patients*

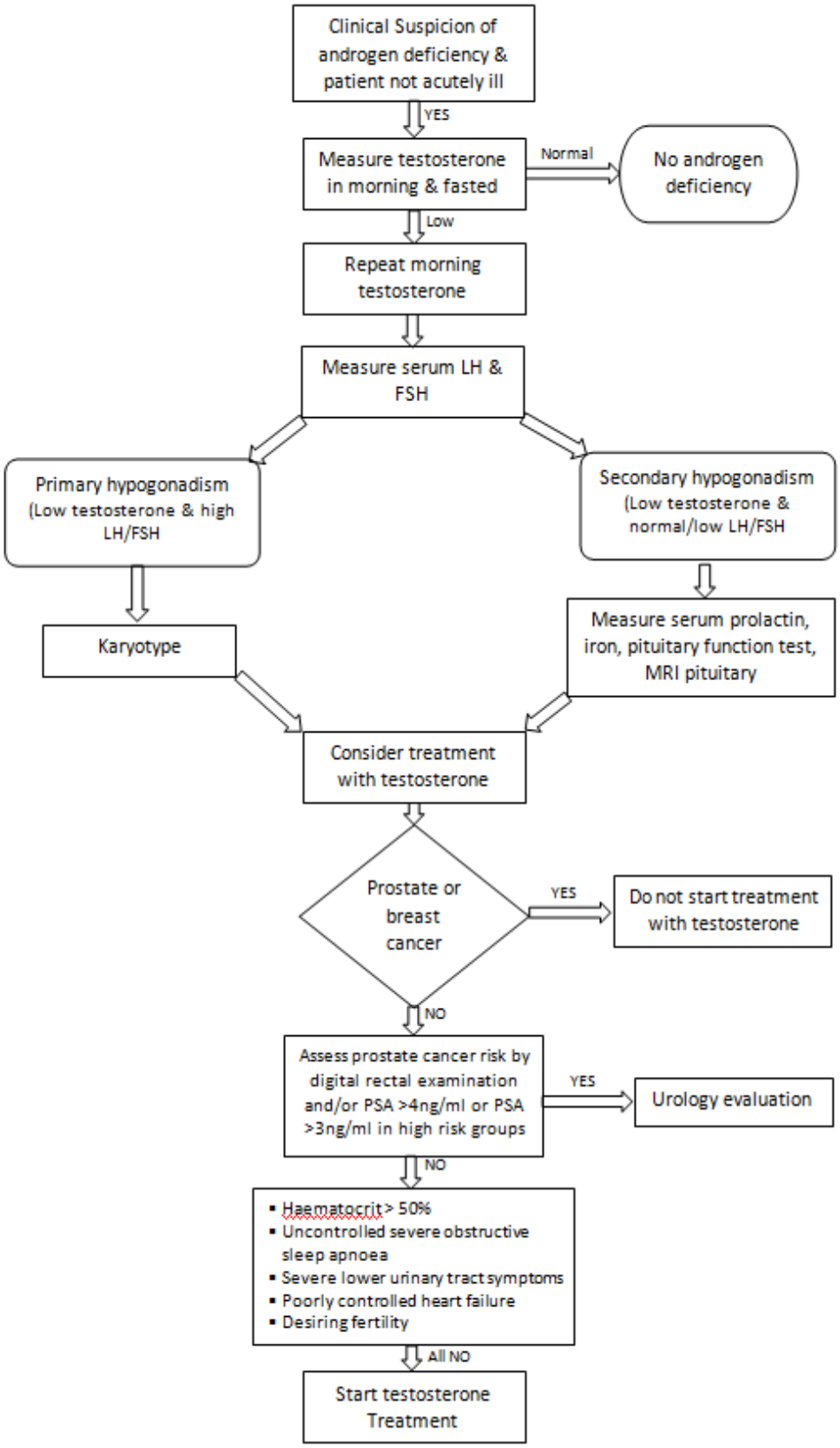
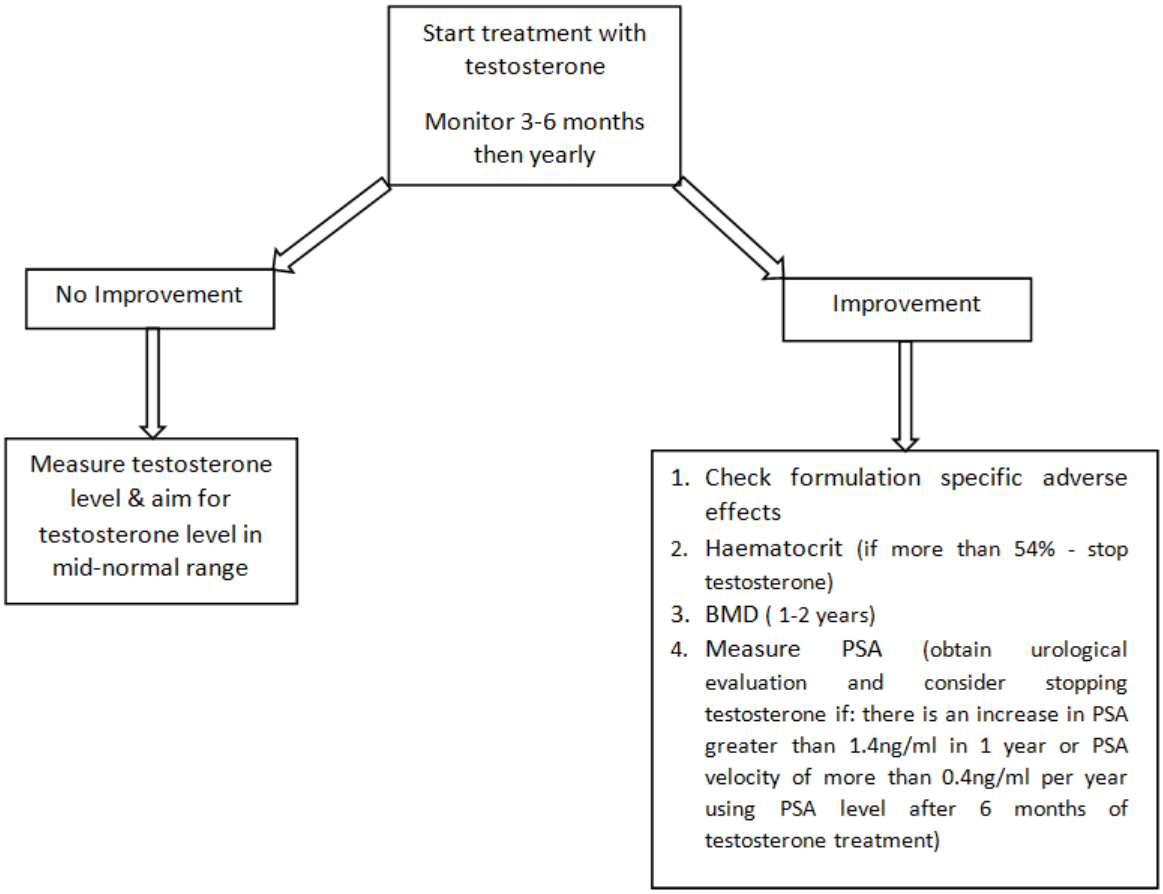


***Figure 9**: Algorithm regarding monitoring after starting testosterone treatment.*



Observations

Areas of good practice:

- Early morning measurement of total testosterone serum levels
- When diagnosing causes of secondary hypogonadism, a full pituitary hormonal profile was requested
- In a significant number of cases of secondary hypogonadism, a form of imaging modality was considered, generally CT or MRI
- No patient who was prescribed testosterone was known to have suffered from breast or prostate cancer.

Areas for improvement:

- Need for improved documentation of the signs and symptoms of hypogonadism
- Need for use of total testosterone testing as a primary diagnostic test, with 2 separate tests serving to confirm hypogonadism
- Karyotyping should be considered in the majority of testosterone deficient patients with primary hypogonadism
- Iron studies should be considered as part of the diagnostic investigations
- Need to take PSA prior to starting treatment in those over 40 years
- Need for shortened follow-up intervals following treatment intervention
- Need for improved documentation of patient symptom alleviation and treatment side effects on monitoring
- Need to perform BMD in all patients prior to starting treatment and follow up accordingly.
- Option to analyse steroids by liquid chromatography and mass spectrometry
- Need to have male normative BMD values for males

Recommendations

This analysis identified the need for documentation of the signs and symptoms and also to repeat testosterone levels prior to starting

treatment. It also identified the need for karyotyping in patients with primary hypogonadism. The results also show the need to measure BMD and PSA before prescribing testosterone. Regarding follow up, this audit recognizes the need for earlier review at 3-6 months with proper documentation of symptoms. Repeat BMD should be done at 1-2 years after treatment initiation. Figure 8 and 9 are two algorithms which one can use when considering testosterone treatment in patients with androgen deficiency. Finally, patients best served by review in a specialist clinic not in the community.

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