The Effectiveness of Clomiphene Citrate Compared to Exogenous Testosterone Therapy in Adult Males

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The Effectiveness of Clomiphene Citrate Compared to Exogenous Testosterone Therapy in Adult Males

Abstract

Background:

Low testosterone (T) in men is a common medical condition affecting approximately 5 million men in the United States. Low T caused by primary hypogonadism is treatable with exogenous testosterone in the form of direct injection or topical gels. However, low T due to secondary hypogonadism is amenable to treatment with exogenous testosterone forms, as well as selective estrogen receptor modulators (SERMs), such as clomiphene citrate (Clomid; CC). There are significant side effects and increased cost with exogenous testosterone therapy (mentioned above) compared to clomiphene. Generic clomiphene, used off-label, avoids these side effects and represents a significant cost savings. But what is its efficacy compared to testosterone therapy?

Methods:

An exhaustive search of available medical literature was conducted utilizing 3 separate, thoroughly vetted search engines, including MEDLINE-Ovid, Web of Science, and CINAHL. Keywords used included: clomiphene, hypogonadotropic hypogonadism, and ADAM or qADAM or quality of life.

Results:

Based on the search criteria, 6 articles were identified and reviewed for relevancy. This was narrowed down to 2 articles that met the inclusion and exclusion criteria. These 2 studies were observational, non-randomized studies. One study found that there was no statistical difference between CC, injected testosterone, or testosterone gel replacement therapy (TGRT) in regards to patient satisfaction as measured with the qADAM questionnaire. The second study found that CC was as effective as TGRT at raising serum T levels at a much lower cost without the same risks of side effects associated with TGRT.

The overall quality of both studies was low and further investigation would need to be done to validate these findings. Specifically, randomized, placebo controlled, double blinded, studies with larger cohorts are necessary.

Conclusion:

Clomiphene citrate has been used for many years in an off-label manner to treat men with hypogonadism, mostly in specialty centers. There are only 2 studies found in the literature comparing CC to exogenous testosterone treatment and both of are low quality. Despite this limitation, and a lack of FDA approval, CC appears to be a viable option for men with low T due to secondary hypogonadism, demonstrating equal improvement in overall patient satisfaction and quality of life improvements at a lower cost while avoiding the potential side effects of testicular atrophy and reduced spermatogenesis.

Keywords: Clomiphene citrate, hypogonadotropic hypogonadism, ADAM, qADAM, quality of life

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Biography

[Redacted for privacy]
Abstract

Background:
Low testosterone (T) in men is a common medical condition affecting approximately 5 million men in the United States. Low T caused by primary hypogonadism is treatable with exogenous testosterone in the form of direct injection or topical gels. However, low T due to secondary hypogonadism is amenable to treatment with exogenous testosterone forms, as well as selective estrogen receptor modulators (SERMs), such as clomiphene citrate (Clomid; CC). There are significant side effects and increased cost with exogenous testosterone therapy (mentioned above) compared to clomiphene. Generic clomiphene, used off-label, avoids these side effects and represents a significant cost savings. But what is its efficacy compared to testosterone therapy?

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Based on the search criteria, 6 articles were identified and reviewed for relevancy. This was narrowed down to 2 articles that met the inclusion and exclusion criteria. These 2 studies were observational, non-randomized studies. One study found that there was no statistical difference between CC, injected testosterone, or testosterone gel replacement therapy (TGRT) in regards to patient satisfaction as measured with the qADAM questionnaire. The second study found that CC was as effective as TGRT at raising serum T levels at a much lower cost without the same risks of side effects associated with TGRT.

The overall quality of both studies was low and further investigation would need to be done to validate these findings. Specifically, randomized, placebo controlled, double blinded, studies with larger cohorts are necessary.

Conclusion:
Clomiphene citrate has been used for many years in an off-label manner to treat men with hypogonadism, mostly in specialty centers. There are only 2 studies found in the literature comparing CC to exogenous testosterone treatment and both of are low quality. Despite this limitation, and a lack of FDA approval, CC appears to be a viable option for men with low T due to secondary hypogonadism, demonstrating equal improvement in overall patient satisfaction and quality of life improvements at a lower cost while avoiding the potential side effects of testicular atrophy and reduced spermatogenesis.

Keywords: Clomiphene citrate, hypogonadotropic hypogonadism, ADAM, qADAM, quality of life
Acknowledgements

[Redacted for privacy]
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List of Abbreviations

CC……………………………………………………………………...….Clomiphene Citrate
Low T……………………………………………………………………....Low Testosterone
TGRT…………………………………………….……..Testosterone Gel Replacement Therapy
LH……………………………………………………………………….Luteinizing Hormone
FSH……………………………………………………………..Follicle Stimulating Hormone
SERM…………………………………………………Selective Estrogen Receptor Modulator

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Appendix B…………………………………………..St. Louis University ADAM Questionnaire
The Effectiveness of Clomiphene Citrate Compared to Exogenous Testosterone Therapy in Adult Males

BACKGROUND

Low testosterone (T) in men is a common medical condition affecting approximately 5 million men in the United States, though it is reported to be under diagnosed. It is estimated that fewer than 10% of men with low T in the US currently receive testosterone replacement therapy. Low T results in decreased muscle mass and strength, decreased libido, decreased sexual performance, symptoms of depression, increased fatigue, osteoporosis, and increased rates of cardiovascular disease, dyslipidemia, diabetes, metabolic syndrome, as well as all-cause mortality. Low serum testosterone in adult males may be due to primary testicular failure, in which the testes fail to produce endogenous testosterone, or secondary hypogonadism (AKA hypogonadotrophic hypogonadism) which is much more common. In secondary hypogonadism, there is hypothalamic suppression of gonadotropin-releasing hormone, which in turn leads to decreased production of LH (luteinizing hormone) by the pituitary gland. LH is a necessary signal for the testes to produce testosterone.

Low T caused by primary hypogonadism is treatable with exogenous testosterone in the form of direct injection or topical gels. However, low T due to secondary hypogonadism is amenable to treatment with exogenous testosterone forms, as well as selective estrogen receptor modulators (SERMs), such as clomiphene citrate (brand name: Clomid). Clomiphene citrate (CC) was first introduced in the 1960s and has become one of the most widely used medications to treat anovulation in women, for which it was originally approved by the United States Food and Drug Association (FDA). Despite not having FDA approval, it has been commonly used to treat male infertility due to hypogonadism. Clomiphene citrate, when prescribed off-label for hypogonadism, blocks the feedback inhibition of estradiol at the hypothalamus, which increases
pituitary release of LH (luteinizing hormone) and FSH (follicle stimulating hormone). LH and FSH in turn stimulate the Leydig and Sertoli cells of the testes to produce serum testosterone and spermatogenesis, respectively. See figure I for a representation of the pituitary feedback control of LH, FSH and testosterone from estrogen (E2). This increase in serum testosterone has led many providers to use CC off-label, not only for male infertility, but also for the symptoms of low testosterone.

Testosterone injections or topical gels have been the mainstay of treatment for low T. Exogenous testosterone effects the hypothalamic-pituitary-gonadal axis (HPG axis) resulting in reduced spermatogenesis, and eventually can lead to testicular atrophy. Reduced spermatogenesis is particularly problematic for men wishing to preserve fertility. There are significant side effects and increased cost with exogenous testosterone therapy (mentioned above) compared to clomiphene. Generic clomiphene, used off-label, avoids these side effects and represents a significant cost savings. Can clomiphene citrate provide effective symptomatic relief compared to exogenous testosterone therapy?

METHODS

An exhaustive search of available medical literature was conducted utilizing three separate, search engines, including MEDLINE-Ovid, Web of Science, and CINAHL. Relevant articles were assessed for quality using the GRADE system. Keywords used to search included: clomiphene, hypogonadotropic hypogonadism, and ADAM or qADAM or quality of life. Eligibility criteria included studies comparing clomiphene citrate vs. exogenous testosterone therapy (IM injection or topical gels) and included study outcomes that measure both serum testosterone levels and subjective symptom measures with the ADAM or qADAM questionnaire. Further more, studies had to be published in the English language. Exclusion criteria included
non-comparative studies, those conducted prior to the year 2000, case studies and systematic reviews. Relevant articles were assessed for quality using the GRADE system.\textsuperscript{8}

**RESULTS**

The search strategy resulted in a six total articles; however, only two met eligibility criteria. Both articles\textsuperscript{6,7} were observational studies and retrospective in nature. See Table I.

**Ramasamy et al**

This study\textsuperscript{7} was a retrospective cross-sectional design in which adult males were treated with either clomiphene citrate, testosterone injections, or testosterone gels for symptomatic hypogonadism (total T less than 300ng/dl). Patients reported satisfaction with their treatment regimen using the qADAM questionnaire. The qADAM questionnaire consists of 10 questions related to the symptoms of hypogonadism. Patients score each question with a possible range of 1 to 5, with 1 representing maximal symptoms and 5 represents complete absence of symptoms. Total qADAM score can range from 10 to 50, with a lower score indicating more severe hypogonadal symptoms.\textsuperscript{9} Pre and post treatment serum testosterone and estradiol levels were measured for efficacy. There were 93 patients who were age matched from a retrospective cohort of 1150 men on testosterone replacement therapy (TST): 31 on testosterone injections, 31 on topical testosterone gels and, 31 on clomiphene citrate. This was compared to 31 men who received no testosterone therapy at all and had a serum T > 300ng/dl. There was no difference in median age between men taking CC (40.9), T injections (40.5), T gels (43.9) and controls (40.5). Median serum testosterone increases were reported as follows: CC was 247 to 504ng/dl, injected T was 224 to 1104ng/dl, topical T gels was 230 to 412ng/dl (p<0.05). Not surprisingly, men from the control group that did not receive TST, had significantly lower serum T levels than those that did receive TST. Despite a large difference in pre and post treatment serum T levels
between injectable T and CC or T gels, there was not a statistical difference in overall qADAM scores measured at post-treatment: 35 for CC, 39 for injectable T and 36 for T gels (p>0.05). One notable exception from the qADAM questionnaire was that men receiving T injections reported greater libido than men receiving CC (4 vs 3, p <0.04) or T gels (4 vs 3, p = 0.04), or controls (4 vs 3, p <0.01). See Table II.

With the exception of libido, which was significantly higher with the injected T group (p = 0.04), no statistical difference was seen in the qADAM scores of patients treated with CC, injected T, or T gels. This is despite the much higher serum T levels achieved with injected T. As a result, there does not appear to be an overall correlation with supraphysiologic T levels achieved with injected T and symptom relief. Therefore, this study suggests that CC could be as effective as injected and/or topical gel T, while having fewer potential side effects.

The authors discuss some limitations surrounding their study. Primarily, they state the study was limited by its retrospective, cross-sectional design and the fact that pretreatment qADAM values were not available. Serum T levels were drawn at the same time that qADAM questionnaires were collected from patients. However, there was no control over the timing of the patient’s T injections. Patient’s receiving T injections experience a peak and trough effect of serum T, with much higher levels recorded in the first few days post-injection. The authors suggest that the statistically higher serum T levels seen with men in the injected T group could have been due to these men receiving their T injections in the 3 to 4 days prior to their blood draw. They also discuss a lack of specificity in regards to the qADAM questionnaire. This is due to positive responses being possibly correlated to other conditions, such as depression.

Taylor et al
In this retrospective cohort study, 104 male patients with low serum T (defined as serum T < 300ng/dl) or with male infertility were given testosterone gel replacement therapy (39 TGRT) or clomiphene citrate (65 CC) at the discretion of the treating physician. Of the TGRT group, 100% of the patients were being treated for complaints related to hypogonadism. For the CC group, 65% of patients were being treated for complaints related to hypogonadism, whereas 35% were being treated for MI with related symptoms of hypogonadism. For purposes of this study, biochemical efficacy was defined as an elevation of serum T to the mid-normal range. The authors define mid-normal range as a serum T of approximately 550ng/dl. Patients in the CC group were all started at 50mg every other day. They were then titrated up to 100mg every other day, or titrated down to 25mg every other day in order to achieve a mid-normal range serum T. Men taking TGRT were started at dose of 5mg of either 1% Androgel® or 1% Testim® with a similar titration strategy to biochemical efficacy, though the frequency or range of dosing was not disclosed. Males with high pretreatment luteinizing hormone (LH) levels, indicating likely primary testicular failure, were not offered CC, but may have received TGRT instead. This decision was based on the fact that CC works by up-regulating the hypothalamic-pituitary-gonadal axis to increase T production by normally functioning testis in males with secondary hypogonadism. Pre and post treatment ADAM scores were collected on the CC patients only and were obtained via office or telephone interviewing. Patients reported satisfaction with their treatment regimen using the ADAM questionnaire. The ADAM questionnaire consists of 10 questions related to the symptoms of hypogonadism. Each question is assigned 1 point of value for a yes answer, zero points for a no answer. A higher score indicates more severe symptoms compared to a lower score. This should not be confused with the newer qADAM questionnaire, which gives a higher score to patients who have low to absent hypogonadal symptoms. Average age at treatment initiation was 42 for the CC group and 57 for the TGRT
group. Average follow up was 23 months for CC and 46 month for TGRT. Average post
treatment serum T was 573ng/dl for CC and 553ng/dl for TGRT (p < 0.001). This reflected an
average serum T increase of 296ng/dl in the CC group and 332ng/dl in the TGRT group. Both
treatments had statistically significant increases in post treatment serum T. Among CC patients,
the average pre treatment ADAM score was 4.9 and post treatment was 2.1. (P<0.05). ADAM
questions specifically related to sexual function domain was 0.76 vs. 0.23 at follow up (p<0.05).
Ninety-one percent of the patients responded to the ADAM questionnaire with an improved
score compared to pretreatment levels. No adverse events were reported in either group. Monthly
cost of TGRT ranged from $265 to $270, versus CC (50mg every other day) reported at $83.

The authors conclude that compared to TGRT, clomiphene citrate demonstrated
biochemical and clinical efficacy at a lower cost. The authors of this study do not discuss
limitations of their study.

**DISCUSSION**

The mainstay of FDA approved therapy for men with low T caused by both primary and
secondary hypogonadism has been in the form of exogenous testosterone replacement, given as
an intramuscular injection or topical gel. While exogenous T has been proven to be effective at
raising serum T levels and improving symptoms, it does not mimic normal circadian hormone
release. Exogenous T therapy is known to have significant side effects, namely the possibility
of testicular atrophy and infertility due to negative feedback of the hypothalamic-pituitary-
gonadal (HPG) axis. Clomiphene citrate, on the other hand, influences the HPG axis by blocking
feedback estradiol receptors at the hypothalamus, which results in the increased production of
endogenous testosterone by the testes through an increase in LH secretion by the anterior
pituitary gland. This increase in the body’s own endogenous testosterone secondary to administering CC has seemed to reflect restorative effects on the HPG axis.²

While there are only 2 studies found in the literature directly comparing CC to exogenous T therapies, the literature clearly supports the biochemical efficacy of CC treatment in hypogonadism.⁶ As a result of CC’s mechanism of action, it avoids the common side effects experienced with exogenous T therapy. This may be especially important for younger male patients who wish to preserve their fertility.

Currently, CC is only approved by the FDA for the treatment of ovulatory dysfunction in females wishing to become pregnant. Recently, Repros Therapeutics, Inc. has submitted an FDA new drug application for Androxal for the treatment of secondary hypogonadism. Androxal is the single isomer of CC. Currently a decision on approval by the FDA is pending.¹¹

Testosterone injections have to be administered weekly and require patients to be seen in clinic for their injections. This increases costs in addition to the cost of the drug itself. There is also a peak and trough effect of serum T levels experienced by patients receiving intramuscular (IM) testosterone injections. TGRT therapy overcomes this inconsistent serum T level versus IM injections, but carries with it the risk of skin irritation and cross contamination to household members, including children.⁶

Additionally the following costs were recently found via GoodRx.com¹²: TGRT, even in the generic form, ranges from $176 to $344 per month. CC on the other hand, can be purchased for $31 to $45 per month in the 50mg form which can be cut in half, since most patients are prescribed 25mg of CC daily.¹ This brings the monthly cost down to the range of $15.50 to $22.50 per month. It should be noted that drug prices are constantly changing due to
geographic differences as well as generic status changes. But the possible decrease in cost to the patient is still significant.

Ideally, further studies should be conducted in regards to CC for patients with hypogonadism. Both studies\textsuperscript{6,7} reviewed in this analysis were determined to be of very low-quality utilizing the GRADE system. Both studies\textsuperscript{6,7} were retrospective cohort studies and had small sample sizes. Only one study (Ramasamy et al\textsuperscript{7}) performed age matching. Ramasamy et al\textsuperscript{7} disclosed significant funding via pharmaceutical company Repros, which may introduce possible bias related to industry objectives. Frequent off-label use of CC, along with the possible entry of a single isomer of CC to the market (Androxal), will likely shed more light on the use of SERMs for hypogonadism and potentially encourage more studies of higher quality to be conducted.

**CONCLUSION**

Clomiphene citrate has been used for many years in an off-label manner to treat men with hypogonadism, mostly in specialty centers. Of the only 2 studies found in the literature comparing CC to exogenous testosterone treatment, both of are very low quality. Despite this limitation, and a lack of FDA approval, CC appears to be a viable option for men with low T due to secondary hypogonadism, demonstrating equal improvement in overall patient satisfaction and quality of life improvements while avoiding the potential side effects of testicular atrophy and reduced spermatogenesis. Furthermore, a significant cost savings exists for patients treated with CC, though the cost savings is constantly changing. Despite the overall quality of the comparative data found in the literature, enough evidence exists to warrant further research on this drug in order to treat patients with less risks at a lower cost.
References


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### Table I. Characteristics of Reviewed Studies

#### GRADE Quality Assessment

<table>
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<tr>
<th>Study</th>
<th>Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Inconsistency</th>
<th>Publication bias likely</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramasamy et al</td>
<td>Retrospective cross-sectional design</td>
<td>Serious b</td>
<td>None</td>
<td>Serious c</td>
<td>Not serious</td>
<td>Yes d</td>
<td>Very Low</td>
</tr>
<tr>
<td>Taylor et al</td>
<td>Retrospective cohort</td>
<td>Serious e</td>
<td>None</td>
<td>Serious c</td>
<td>Not serious</td>
<td>No</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

*a* Age matched from retrospective cohort of 1,150  
*b* Duration of treatment not mentioned. Timing of serum T measurements was not controlled. Single center. Pretreatment subjective questionnaires were not collected.  
*c* Confidence intervals not mentioned; Small sample size.  
*d* Financial interests and/or other relationship with Auxilium, Endo and Repros.  
*e* Patients were not age matched. ADAM scores only collected on CC group. Decision to treat with CC or TGRT left to treating physician discretion. Single center.

### Tables II - III. Summary of Findings

#### Table II. Ramasamy et al

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Injected T (n=31)</th>
<th>Gel (n=31)</th>
<th>CC (n=31)</th>
<th>Control (n=31)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>40.5 +/- 9.2</td>
<td>43.9 +/- 13.7</td>
<td>40.9 +/- 9.4</td>
<td>40.5 +/- 10.4</td>
<td>p &gt;0.05</td>
</tr>
<tr>
<td>Pre treatment serum T (ng/dl)</td>
<td>223.5 +/- 182.5</td>
<td>230.0 +/- 151.0</td>
<td>247.0 +/- 66.5</td>
<td>310.0 +/- 136.0</td>
<td>p &gt;0.05</td>
</tr>
<tr>
<td>Post treatment serum T (ng/dl)</td>
<td>1,104.0 +/- 866.5</td>
<td>412.0 +/- 339.0</td>
<td>503.5 +/- 306.8</td>
<td>503.5 +/- 306.8</td>
<td>p &lt;0.05</td>
</tr>
<tr>
<td>Change in serum T (ng/dl)</td>
<td>956 +/- 879.0</td>
<td>243.0 +/- 375.5</td>
<td>371.5 +/- 325.8</td>
<td>371.5 +/- 325.8</td>
<td>p &lt;0.05</td>
</tr>
<tr>
<td>qADAM (range 10-50)</td>
<td>39 +/- 8</td>
<td>36 +/- 9</td>
<td>35 +/- 8</td>
<td>34 +/- 9</td>
<td>p &gt;0.05</td>
</tr>
<tr>
<td>Libido question from qADAM (range 1-5)</td>
<td>4.0 +/- 1.0</td>
<td>3.0 +/- 1.0</td>
<td>3.0 +/- 1.0</td>
<td>3.0 +/- 1.5</td>
<td>p &lt;0.05</td>
</tr>
</tbody>
</table>

#### Table III. Taylor et al

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Gel (n=39)</th>
<th>CC (n=65)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57 (30 – 78)</td>
<td>42 (19 – 70)</td>
<td>p &lt;0.05</td>
</tr>
<tr>
<td>Average follow up</td>
<td>46 months (range 6 – 149)</td>
<td>23 months (range 8-40)</td>
<td>p &lt;0.05</td>
</tr>
<tr>
<td>Average Pre treatment serum T (ng/dl)</td>
<td>221 (27 – 363)</td>
<td>277 (16 – 381)</td>
<td>p &lt;0.05</td>
</tr>
<tr>
<td>Average Post treatment serum T (ng/dl)</td>
<td>553</td>
<td>573</td>
<td>p &lt;0.05</td>
</tr>
<tr>
<td>Average Change in serum T (ng/dl)</td>
<td>332</td>
<td>296</td>
<td>p &lt;0.05</td>
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<tr>
<td>Average pre treatment ADAM score</td>
<td>__</td>
<td>4.9</td>
<td>p &lt;0.05</td>
</tr>
<tr>
<td>Average post treatment ADAM score</td>
<td>__</td>
<td>2.1</td>
<td>p &lt;0.05</td>
</tr>
<tr>
<td>Pre treatment sexual function questions from qADAM</td>
<td>__</td>
<td>0.76</td>
<td>p &lt;0.05</td>
</tr>
<tr>
<td>Post treatment sexual function questions from qADAM</td>
<td>__</td>
<td>0.23</td>
<td>p &lt;0.05</td>
</tr>
</tbody>
</table>
Figure I. Pituitary feedback control of LH, FSH and Testosterone from Estrogen (E2). Diagram is courtesy of Dr Rochira.\textsuperscript{14}

[Figure redacted for online publication due to copyright.

See Figure 5 here: \url{http://www.eje-online.org/content/155/4/513.figures-only}]
Appendix A. – qADAM Questionnaire

Questions Used as Part of the qADAM Questionnaire

1. How would you rate your libido (sex drive)?
   1(terrible) 2(poor) 3(average) 4(good) 5(excellent)

2. How would you rate your energy level?
   1(terrible) 2(poor) 3(average) 4(good) 5(excellent)

3. How would you rate your strength/endurance?
   1(terrible) 2(poor) 3(average) 4(good) 5(excellent)

4. How would you rate your enjoyment of life?
   1(terrible) 2(poor) 3(average) 4(good) 5(excellent)

5. How would you rate your happiness level?
   1(terrible) 2(poor) 3(average) 4(good) 5(excellent)

6. How strong are your erections?
   (1= extremely weak 5= extremely strong)
   1 2 3 4 5

7. How would you rate your work performance over the past 4 weeks?
   1(terrible) 2(poor) 3(average) 4(good) 5(excellent)

8. How often do you fall asleep after dinner?
   1(never) 2(1-2/week) 3(3-4/week) 4(5-6/week) 5(every night)

9. How would you rate your sports ability over the past 4 weeks?
   1(terrible) 2(poor) 3(average) 4(good) 5(excellent)

10. How much height have you lost?
    1(2" or more) 2(1.5-1.9") 3(1-1.4") 4(0.5-0.9") 5(none-0.4")
Appendix B. – St. Louis University ADAM Questionnaire

Questions Used as Part of the Saint Louis University ADAM Questionnaire

1. Do you have a decrease in libido (sex drive)?

2. Do you have a lack of energy?

3. Do you have a decrease in strength and/or endurance?

4. Have you lost height?

5. Have you noticed a decreased “enjoyment of life”?

6. Are you sad and/or grumpy?

7. Are your erections less strong?

8. Have you noted a recent deterioration in your ability to play sports?

9. Are you falling asleep after dinner?

10. Has there been a recent deterioration in your work performance?

NOTE. A positive questionnaire result is defined as a “yes” answer to questions 1 or 7 or any 3 other questions.