Erectile Dysfunction and Low Testosterone: Findings in a Cohort of Barbadian Diabetic Males

Dr. Diane Brathwaite
M.B.B.S (UWI) , MRCP (London), MSc Diabetes, MSc Endocrinology
Clinical Coordinator
The Diabetes Centre Warrens, St.Michael

Acknowledgements

Dr. Laura Layne
Natalia Parris
The Barbados Diabetes Foundation
All the willing participants

Thanks to Professor Hugh Jones
(Professor of Andrology at Sheffield Teaching Hospital)


THE DARK KNIGHT RISES.....HMMM?
BEARMAN

Background

- The Diabetes Centre May 2014
- Multidisciplinary Care Centre
- Diabetes and Metabolic Syndrome
- Referrals: MOH and Private
- MOH: May 2014- August 2016
- 458 referrals
- 74% Females
- 26% males

Preliminary Observations

- Audit: May 2014 to June 2015
- 50% of the population was obese
- 25% overweight.
- Majority clients (34.55%) were 50-59 yrs.
- Hypertensive: 121 (45.66%)
- Dyslipidemia: 106 (38.11%)
- Average BMI 30.86% (75 % population overweight or obese)
- Average waist circumference 102 cm

Most Common Complaint among males ????

"… Doc …. it don't WORK ! "

Preliminary Observations:
Help seeking behavior

A pilot survey in men during preliminary preparations for this study revealed that many men did not seek professional help but relied more on alternative medicine, advice from friends and black-market sourced medications. Further understanding of this issue from the patients' perspective is necessary.

- Erectile Dysfunction and Hypogonadism are areas under increased investigation and discussion today.
- Low testosterone, hypogonadotrophic hypogonadism (HH) and erectile dysfunction (ED) become increasingly common in males
- Associated health risk.
- Could have significant implications for healthcare systems and financial planning.
- Should Androgens be routinely measured?
  - ✓ The Endocrine Society in the United States, recommends the measurement of testosterone in patients with Type 2 diabetes on a routine basis (Bhasin et al. 2006).
  - ✓ Not part of The American Diabetes Association or The Diabetes Centre's Guidelines.
  - ✓ Perry-Keene (2014) utilisation of testosterone levels for making treatment decisions is flawed especially in asymptomatic people.
  - ✓ Are these recommendations practical?

DO I Or DO I NOT TEST ANDROGEN LEVELS?

WHATS THE BIG DEAL ?

WHAT EXACTLY IS GOING?

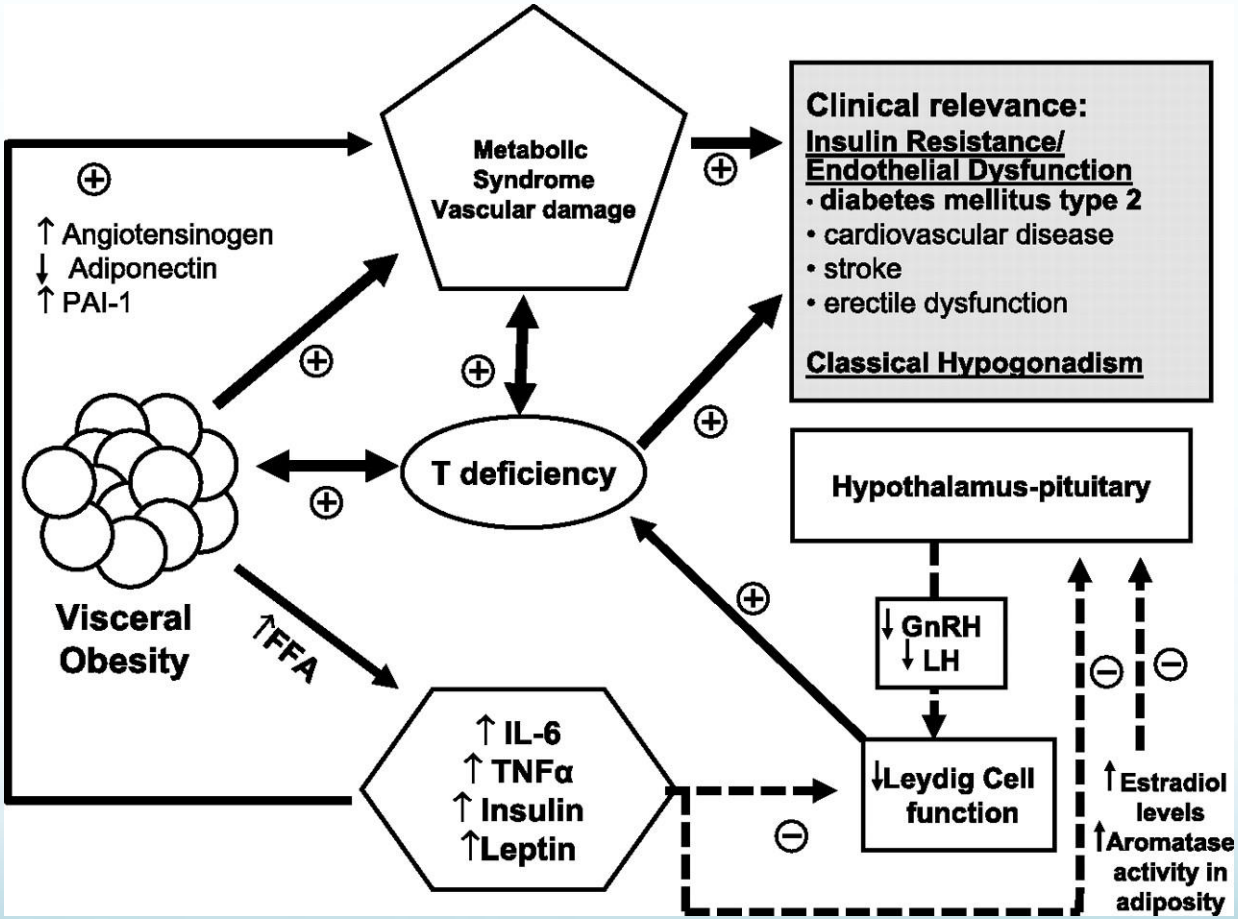
Literature Review
Erectile Dysfunction

- Erectile dysfunction (ED) “the inability to achieve and maintain an erection sufficient to permit satisfactory sexual intercourse” (NIH Consensus Conference 1993).
- ED is common in diabetic males
- 71 percent Penson and Wessels (2004).
- The Look Ahead Study (Rosen et al. 2009), mild to moderate reported ED of 49.8% among men with DM.
- occurs at an earlier age and more frequently in diabetics compared to non-diabetics (Lindau et al.2010) (De Berardis et al. 2002).
- Men with ED much higher risk of having undiagnosed DM

Erectile Dysfunction

- autonomic dysfunction
- obliterative vascular disease.
- **endothelial dysfunction
- obesity and androgen deficiency create pro-inflammatory states and endothelial dysfunction
- ED is an early indicator of CVD

Pathobiology of Obesity and Low Testosterone States



Literature Review
Low Testosterone

- The European Association of Urology “Hypogonadism should really be considered as a clinical syndrome of low testosterone associated with symptoms (Dhole al.2015).
- Hypogonadism
- Overt or Borderline Kapoor D. et al. (2006).
  - Overt hypogonadism :clinical symptoms and low testosterone level (total testosterone <8 nmol/l and/or bioavailable testosterone <2.5 nmol/l).
  - Borderline hypogonadism is the presence of symptoms and total testosterone of 8-12 nmol/l or bioavailable testosterone of 2.5-4 nmol/l.
- Common in Type 2 Diabetes.
- Corona et al. showed that in men with ED, testosterone levels were low (<10.4) in “24.5% of men with diabetes versus 12.6% of nondiabetic subjects after adjustment for age and BMI.”
- Dhindsa et al. (2004) 33% of Type 2 diabetics hypogonadal.

- vicious bidirectional self-perpetuating cycle exists between obesity and low testosterone
- interplay between insulin sensitivity, triglycerides, and sex steroids is almost immediate as supported by glucose clamp studies
- Lapauw et al. (2011) showed that increasing testosterone and decreasing estradiol levels for 1 week improved
  - ✓ postprandial triglyceride handling
  - ✓ postprandial glucose-dependent insulinotropic polypeptide (GIP) release
  - ✓ insulin sensitivity".
  - ✓ So managing androgen deficiency appropriately has significant short-term benefits.

Low Testosterone

- low HDL- lipoprotein
- raised LDL- lipoprotein
- independently associated with an increase in all-cause mortality and CVD
- Kapoor (2007) testosterone status is essential in the management of men with ED: testosterone replacement therapy “converts 60% of sildenafil non-responders into responders”.

Study Hypotheses:

- Low Testosterone in males referred from the polyclinics attending the Diabetes Centre is age and body mass index (BMI) related.
- ED is exceedingly common among Barbadian males attending the Diabetes Centre.
- Health-seeking behavior for ED is diverse.

Objectives

- The prevalence of ED and Low Testosterone in Diabetic males attending The Diabetes Centre between February 2016 –May 2016 was determined.
- The severity of ED was classified by symptomatology using the International Index of Erectile Dysfunction Questionnaire (IIED-5) (See Attached).
- The relationship between patient age, duration of diabetes, BMI, waist circumference.
- Relationships analysed with Regression Analysis and Pearsons Coefficients
- The prevalence of statin and aspirin use in patients at the time of first presentation was evaluated.
- Several aspects of help-seeking behavior in patients with ED were evaluated through direct interviews with four patients in different age ranges.

- **Inclusion Criteria:**
- Consenting males 18-80 years presenting as public patients attending between 28th February to June 16th 2016 were eligible for the study.

- **Exclusion Criteria:**
- Males not referred from the public health care system.
- Males outside the specified age range
- Males not wishing to, or unable to have ED and Testosterone screening done
- Males not attending screening clinic appointment on more than 2 occasions by pre-arranged appointments without good reason, who also failed to comply with requested rescheduling.
- Protracted or serious acute illness.
- Patients on oral or injectable steroid or antiandrogens.

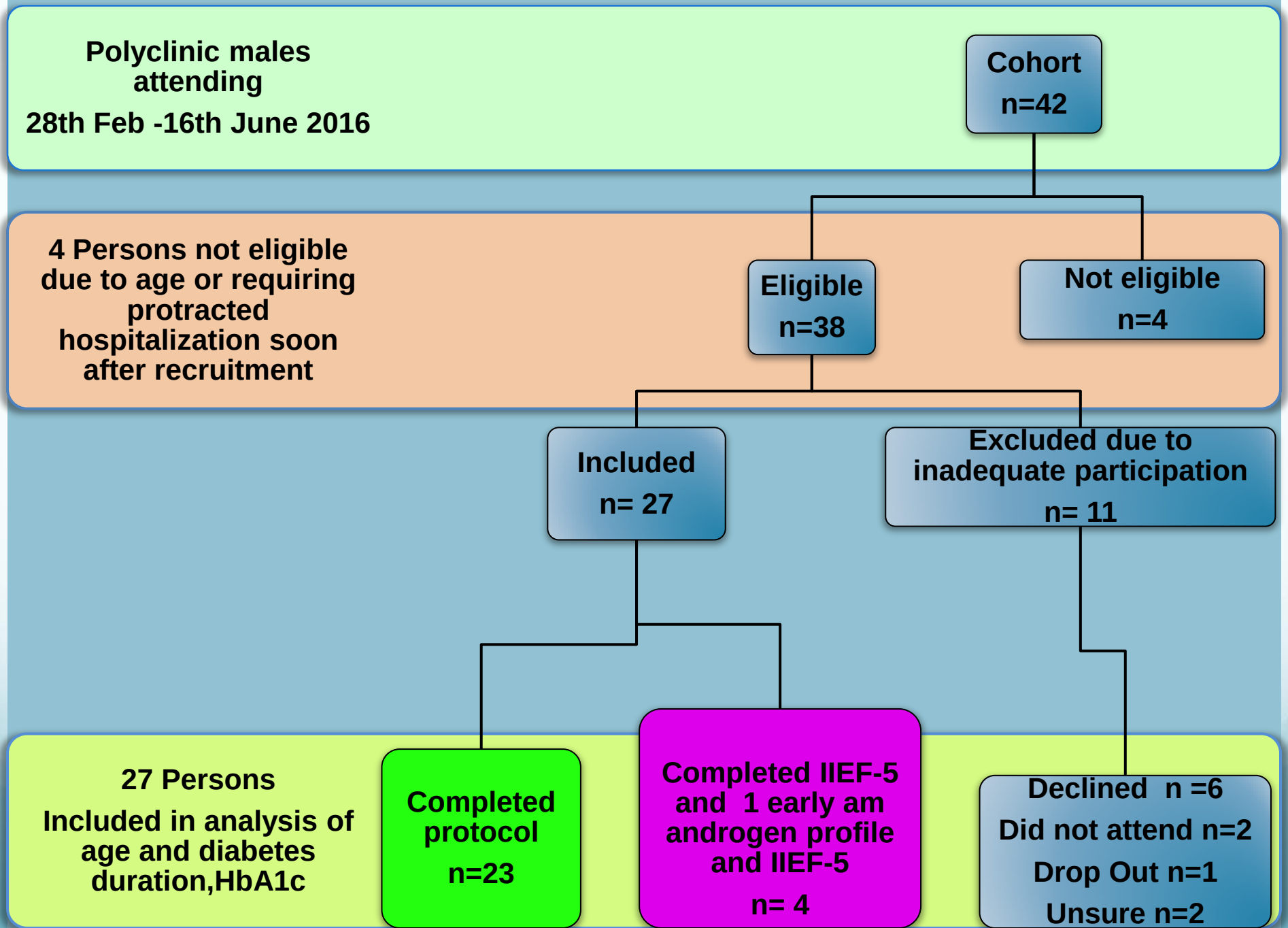
Methodology

Male polyclinic clients:

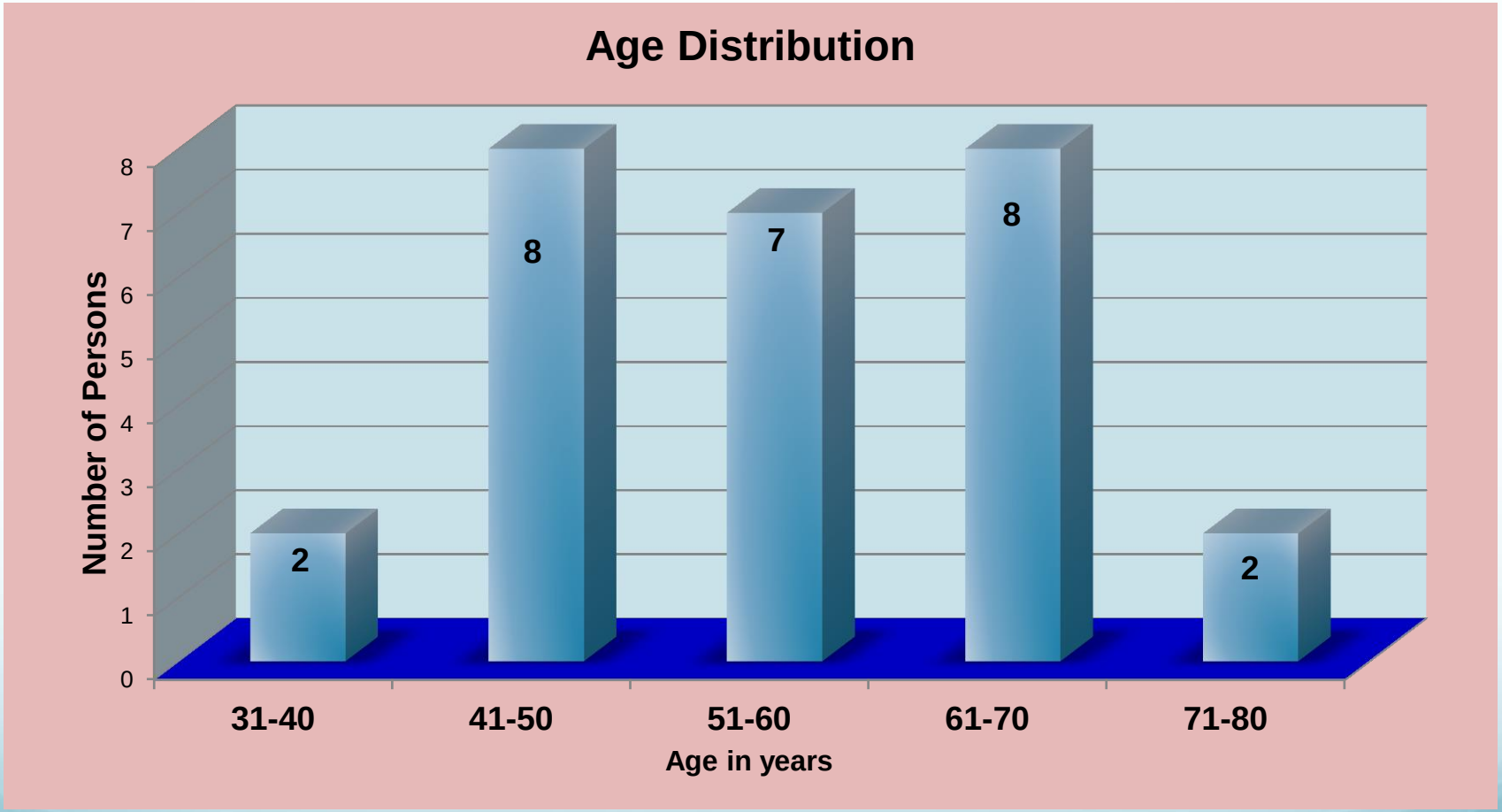
- were assessed for age, BMI, waist circumference and HbA1c
- referred to a newly formed early morning screening clinic.
- Fasting lipids and early am Androgen profile, IIEF-5 screening (Erectile Dysfunction Screening Proforma).
- seen by one of two health care providers.

- Those with subnormal testosterone levels were advised on lifestyle modification and had treatments to improve glycemic control
- 6 week follow up: A repeat early am (8-10am) androgen profile, LH, FSH, Sex Hormone binding globulin, prolactin, ferritin and PSA if not already done.
- Patients further individually counselled at their follow up routine medical visit (0, 3 and 6 months).
- Treatment with androgen replacement was not part of the screening clinic.

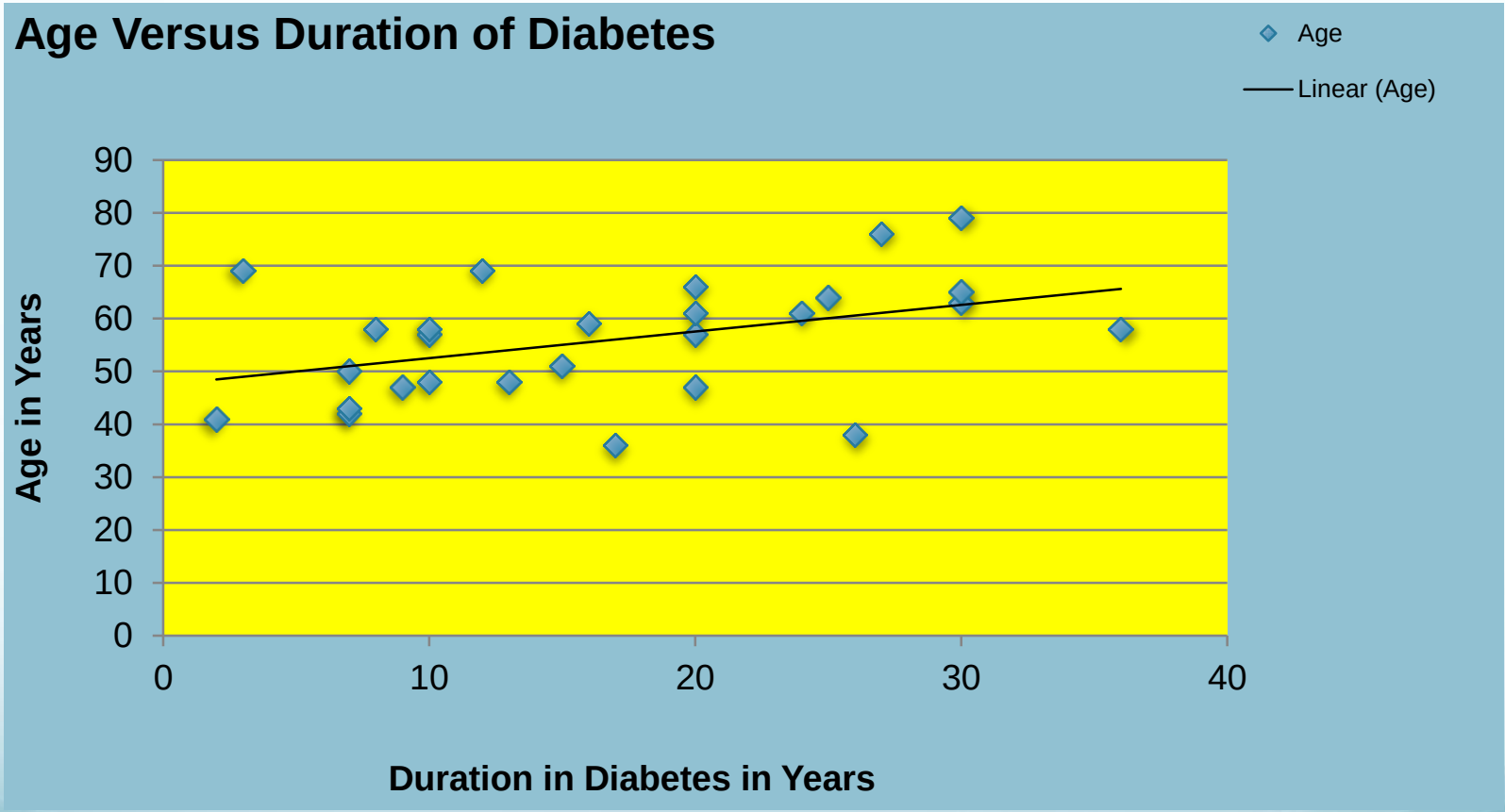
- Patients were treated for ED with PDE5 inhibitors if desired. Non-responders were referred to the appropriate specialist.
- Patients with ED and testosterone levels consistently< 8nmol/L were referred to the hospital endocrine clinic for further evaluation and management.
- Patients with testosterone levels between 8-12nmol/L were advised further on lifestyle modification , need for weight reduction and advised to have a follow up androgen profile with their GP post discharge in 3 months (indicated in their discharge letter).
- Advice was sent to the GP in relation to participation in the study and recommended follow up management/referral options at the end of the study.
- Four males with ED were individually interviewed using a health seeking behavior questionnaire tool (adapted from Zang et al.2014)


Polyclinic males attending
28th Feb -16th June 2016
Cohort n=42
4 Persons not eligible due to age or requiring protracted hospitalization soon after recruitment
Eligible n=38
Not eligible n=4
Included n= 27
Excluded due to inadequate participation n= 11
27 Persons
Included in analysis of age and diabetes duration,HbA1c
Completed protocol n=23
Completed IIEF-5 and 1 early am androgen profile and IIEF-5 n= 4
Declined n =6
Did not attend n=2
Drop Out n=1
Unsure n=2

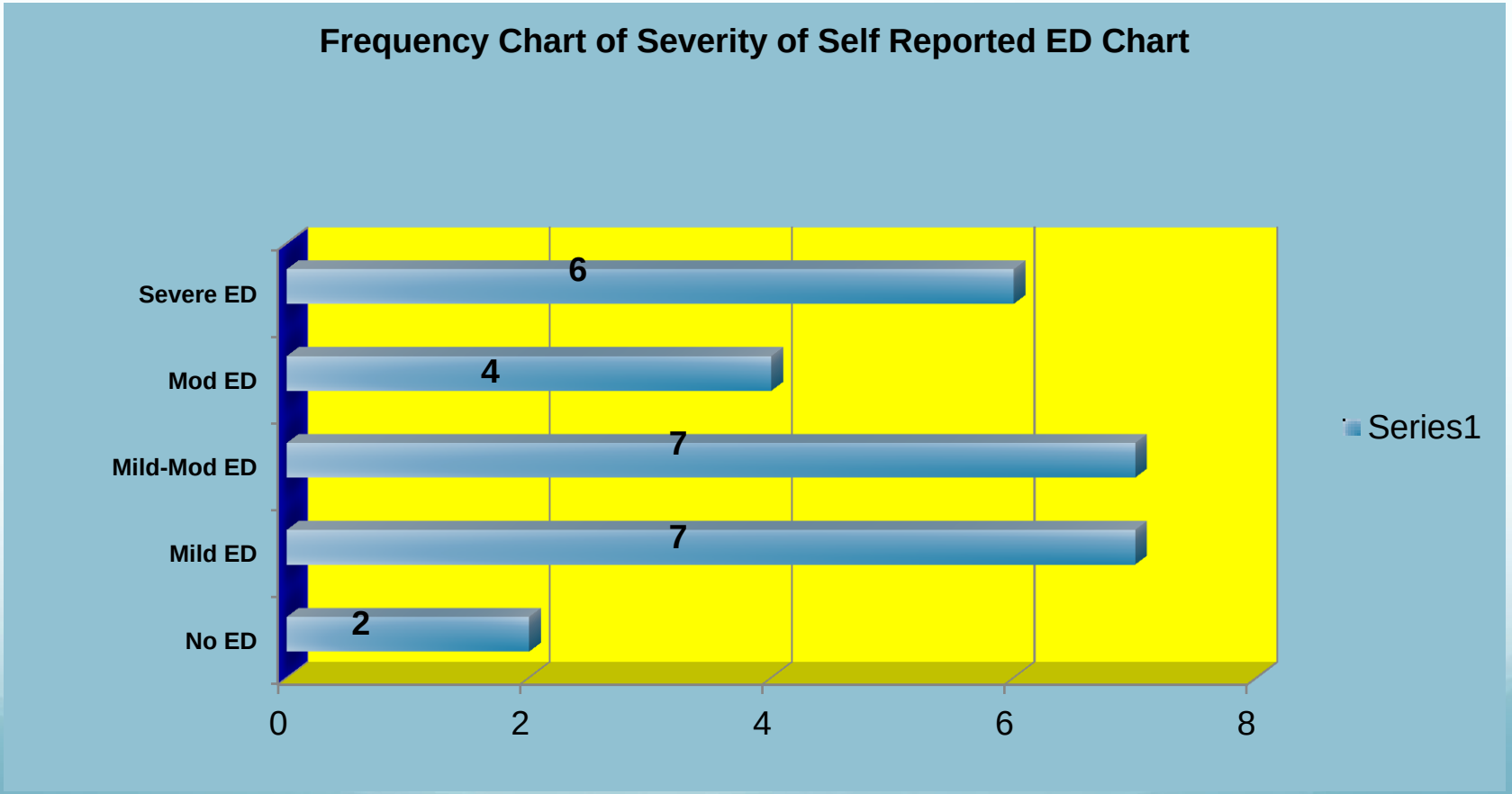
FINDINGS

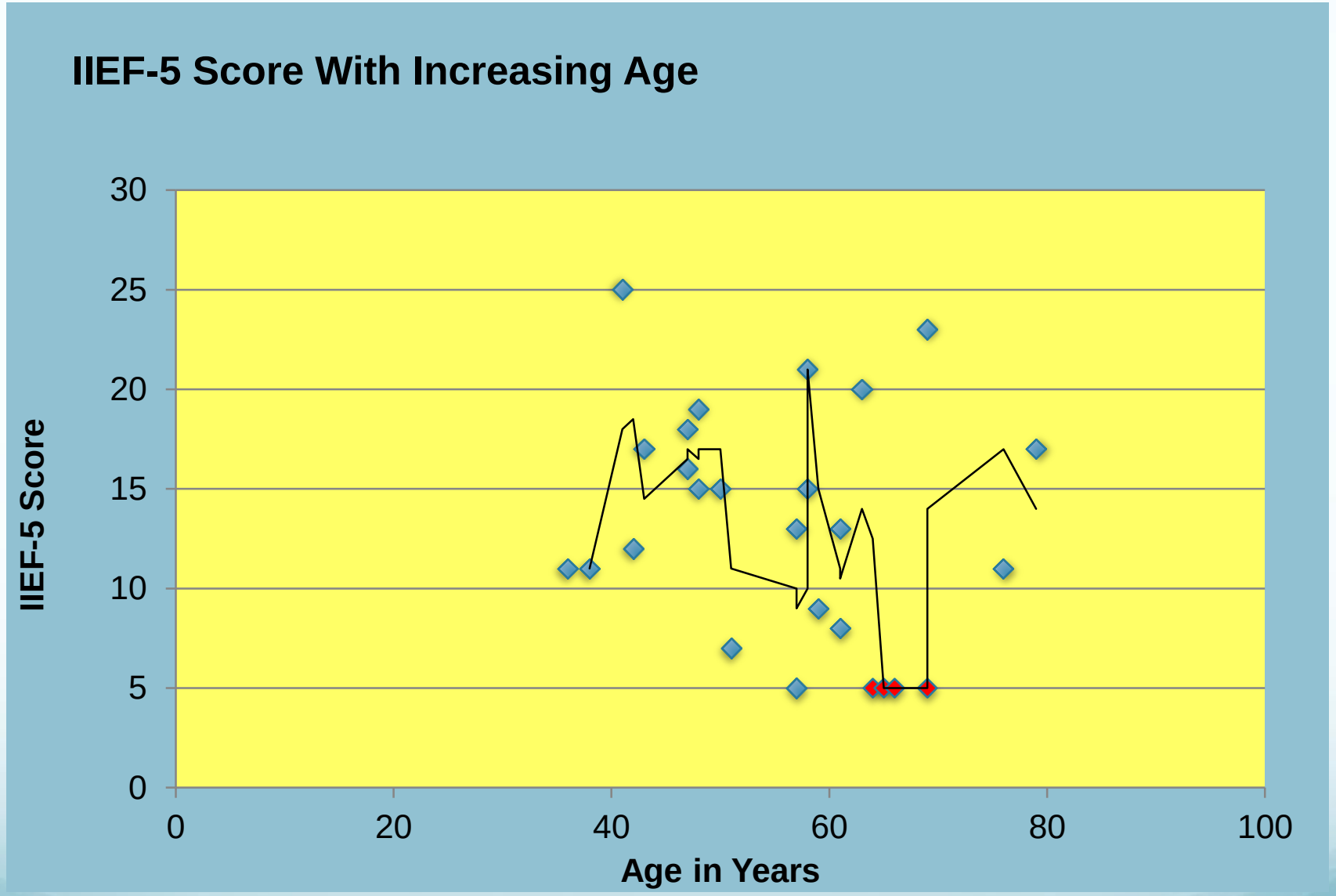

Age Distribution
Number of Persons
0
1
2
3
4
5
6
7
8
2
8
7
8
2
31-40
41-50
51-60
61-70
71-80
Age in years

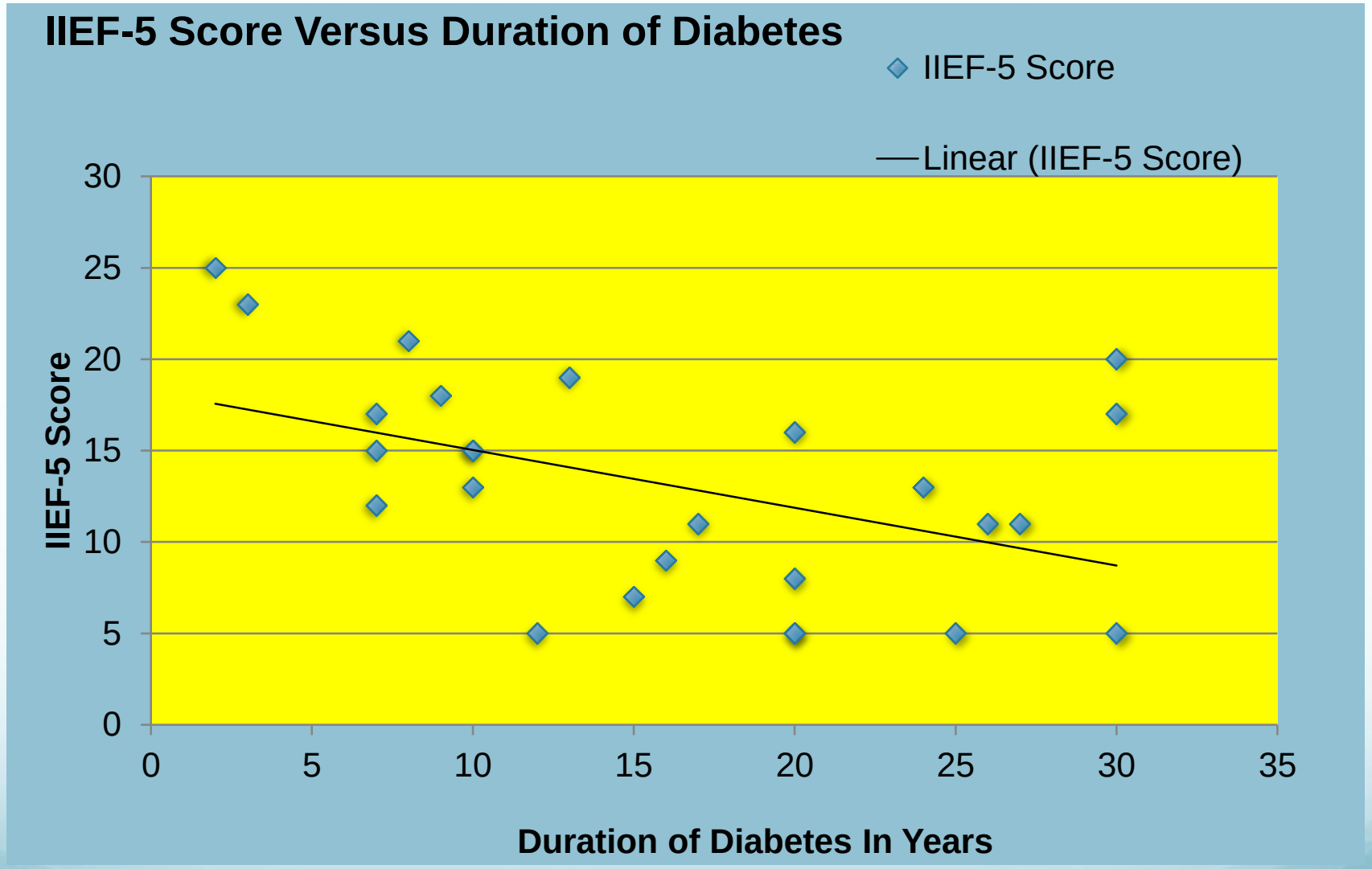
- average duration of diabetes was 16.81 years and all but one of the participants had Type 2 diabetes (there was one Type 1 diabetic in the cohort).

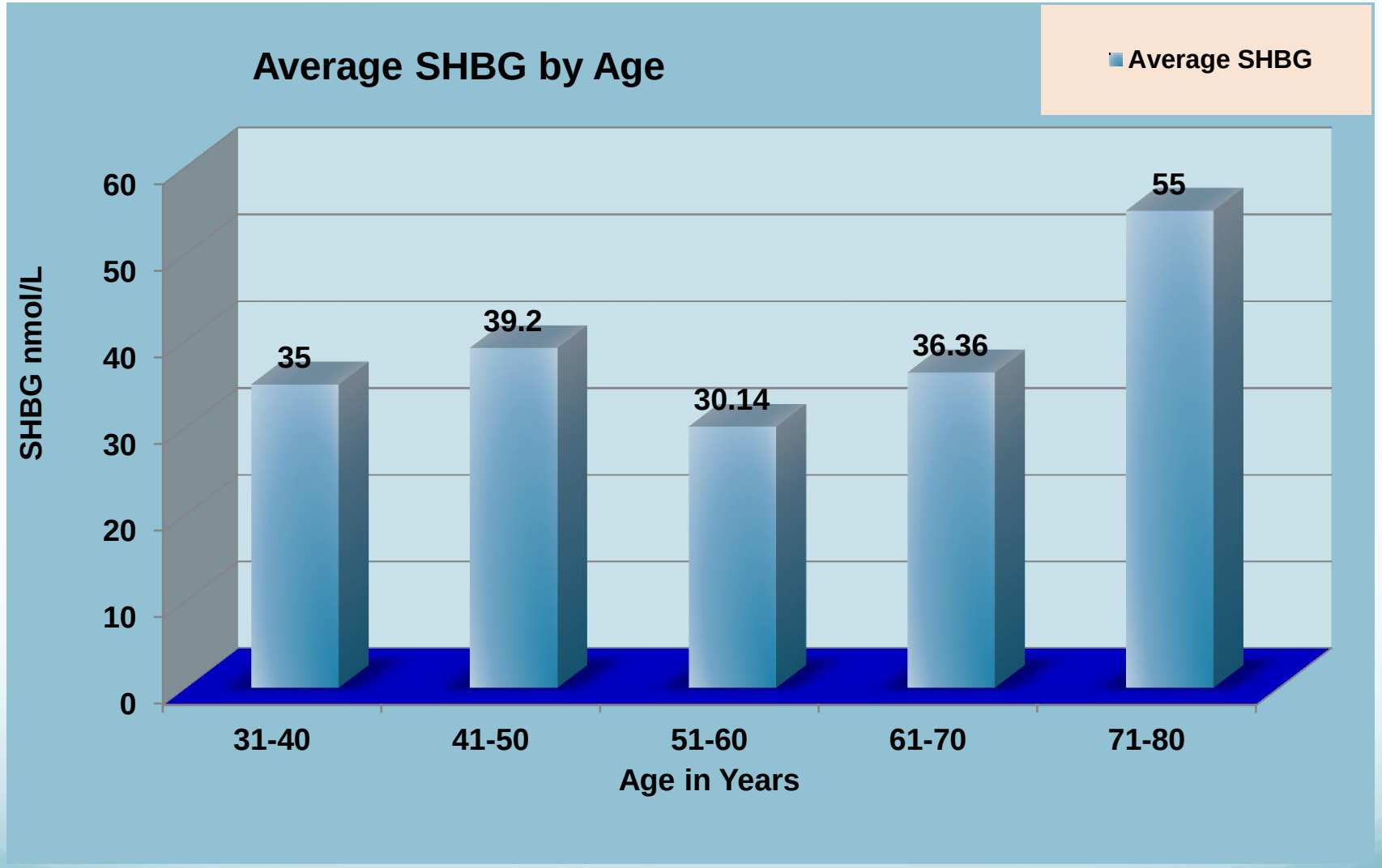


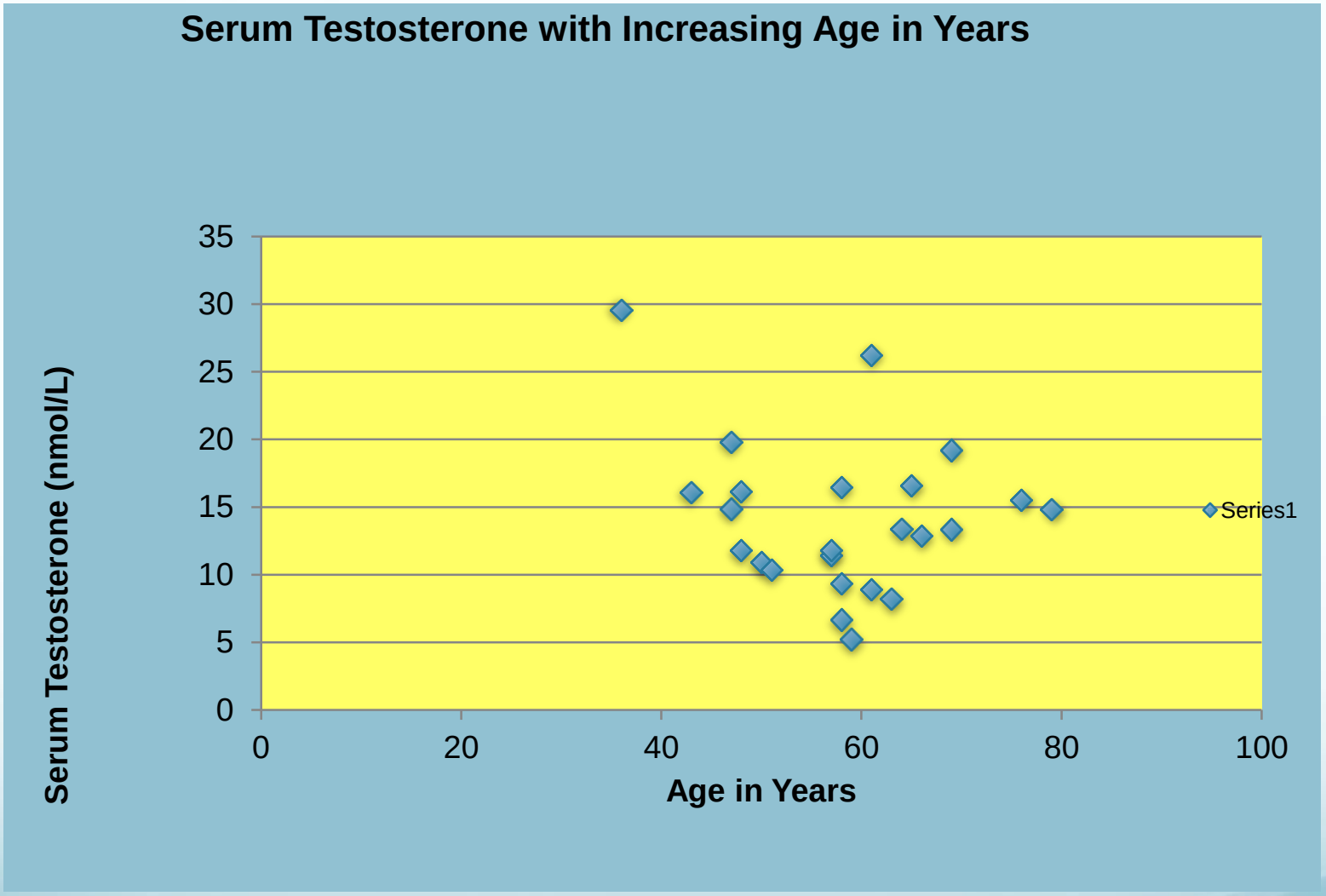
- Ninety-two (92%) reported ED



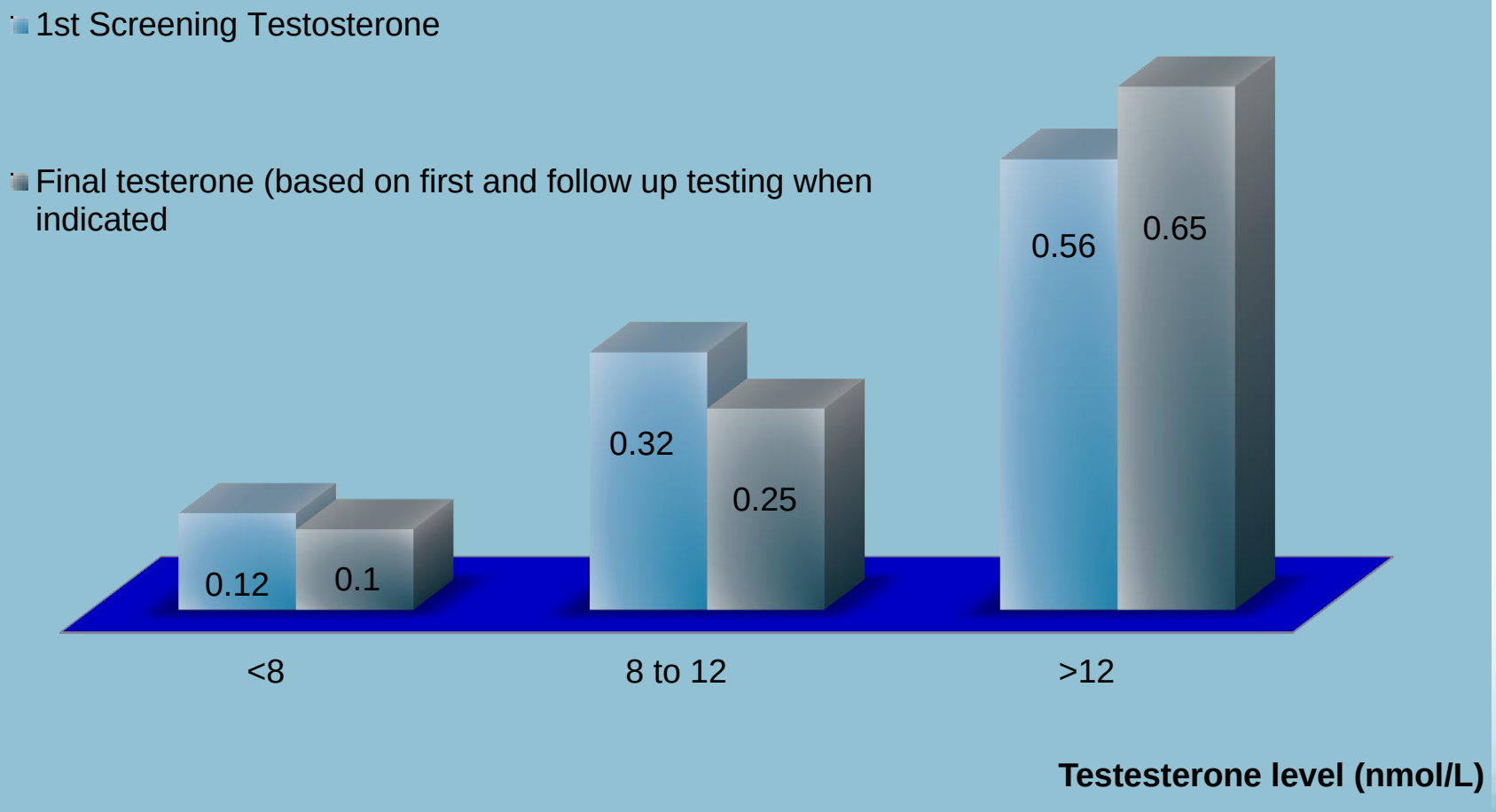

IIEF-5 Score With Increasing Age
IIEF-5 Score
30
25
20
15
10
5
0
0
20
40
60
80
100
Age in Years


IIEF-5 Score Versus Duration of Diabetes
IIEF-5 Score
Linear (IIEF-5 Score)
IIEF-5 Score
0
5
10
15
20
25
30
35
Duration of Diabetes In Years


Average SHBG by Age
Average SHBG
SHBG nmol/L
60
50
40
30
20
10
0
35
39.2
30.14
36.36
55
31-40
41-50
51-60
61-70
71-80
Age in Years


Serum Testosterone with Increasing Age in Years
Serum Testosterone (nmol/L)
35
30
25
20
15
10
5
0
0
20
40
60
80
100
Age in Years
Series1

Comparative Proportion of Persons with Various Testosterone Ranges



Aspirin and Statin Use

- **66.7% of patients with ED were already on aspirin at the time of presentation, while 18/24 persons or 75% of patients with ED were on a statin**

Findings

- ✓ **Weak positive statistically significant relationship between BMI and SHBG .**
- ✓ **Weak Positive correlation between BMI and serum testosterone.**
- ✓ **Weak positive correlation between waist circumference and serum testosterone .**
- ✓ **Weak positive relationship between severity of ED and duration of diabetes.**
- ✓ **No statistically significant relationship between IIEF-5 score and the patient's BMI.**
- ✓ **No statistically significant relationship between BMI and Severity of ED**
- ✓ **There is no statistically significant relationship between waist circumference and IIEF-5 score**
- ✓ **There is no relationship between waist circumference and severity of erectile dysfunction**
- ✓ **A scatter plot showed a wide variation between IIEF-5 scores and duration of diabetes**

HELP SEEKING BEHAVIOR

- Sources of Information: Doctor, Other sources of information were the local pharmacist, friends, and assistants in the health shops.
- primary care provider initiated the discussion
- Marital Status affected comfort level
- Only one of the participants had used sildenafil, another two had tried “natural remedies” from the health shop such as, “Arouse, C.J Max, Meringa, Stone and LGR”

- concerns that finding effective treatment products from the health shop was difficult.
- None of the participants were actively on any regular erectile function enhancers, whether prescribed or off the shelf.
- Wanted more information about ED, and had only been told pharmaceutical options for management existed but felt much more education was needed
- Those getting advice from their doctors said the treatment options were not well explained and they didn’t really get enough information on the recommended treatment.
- Furthermore, the need to purchase of the medication was a deterrent, as treatments for ED are not covered by the Barbados Health Service.

- source of significant embarrassment.
  - affected their ability to engage non-physically with members of the opposite sex
  - less likely to want to talk to a care provider about their ED.
  - try his best not to think about it, but it is a source of great concern for another two.
- “he had his life and there is not much he can do about it.”

- In relation to the care providers:

- ✓ *“they needed to be professional, friendly and helpful while addressing this sensitive topic, as they would any other medical condition. It should not be treated as a joke or insignificant problem”*

Recommendations

- Need for further local research
- Larger studies on ED and low testosterone
- Healthcare cost analysis
- Education and Sensitization Care Providers and Patients
- Local Consensus Committee
- Appropriate Referral
- National Awareness Program
- Drug Service Policies

Possible Further Studies

- Recruit for a larger study of ED and Low Testosterone in Polyclinic Diabetic Males. A refined protocol will be recommended.
- If Funding Available Recruit Cohort from one central and one rural polyclinic
- Identification of the prevalence of ED and HH in our diabetic and non-diabetic male population.
- Cardiovascular Assessment of a small cohort of diabetic males with ED under the age of 50 years for IHD
- Look at impact of 12 week exercise and or weight reduction on total, bioavailable and free testosterone, and sex hormone binding globulin in male Type 2 diabetes with low screening testosterone .
- In-depth enquiry into the use of Alternative Treatments for Male Erectile Dysfunction'
- Quantitative Health Seeking Practises Study for ED in males under the age of 50 in Barbados. A Diabetic and non-Diabetic Arm could be recruited . A socioeconomic analysis of participants would be desired as one of the objectives.
- Evaluation of the Outcome of Male Sexual Education Outreach in Community Centres or Churches in Barbados.
- Psychological Audit in Population of Males with Erectile Dysfunction
- Attitudes and Knowledge of Health Care Providers and Health Advisors in Health Shops to Male erectile Dysfunction
- Attitudes of Females in Barbadian Society to Male Sexual Dysfunction

References

- Anjang et al. 2013. Help seeking behaviour among men with erectile dysfunction in primary care setting , Journal of Men's Health, 8(S1): S94-S96.
- Barbados Today, 2016, Diabetes a serious threat to Barbados, (Available online at http://www.barbadostoday.bb/2015/06/14/diabetes-a-serious-threat-to-barbados/), (Retrieved 30th June 2016)
- Bhasin S. et al. 2006, Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society Clinical Practice Guideline. Journal of Clinical Endocrinology and Metabolism ,91:1995–2010.
- Brand et al.2011. Testosterone, sex hormone-binding globulin and the metabolic syndrome: a systematic review and meta-analysis of observational studies. International Journal of Epidemiology, 40:189–207, (available online http://ije.oxfordjournals.org/content/40/1/189?ijkey=ecf83a412702d1278afa084a8ce0559ee5512773&keytype2=tf_ipsecsha), (Retrieved 18th June 2016)
- Chitaley et al. 2009 Diabetes, Obesity and Erectile Dysfunction:Field Overview and Research Priorities, Journal of Urology, 182(6 supple):s45-s50
- Corona G.et al, 2006, Association of hypogonadism and type II diabetes in men attending an outpatient erectile dysfunction clinic. International Journal of Impotence Research,18:190–197
- Cornally and McGarthy, 2011, Help-seeking behaviour: a concept analysis, International Journal of Nursing Practise, 17(3);280-288
- Berardis et al. 2002. Erectile dysfunction and quality of life in type 2 diabetic patients: a serious problem too often overlooked. Diabetes Care 2002;25:284–291. (Available online at http://care.diabetesjournals.org/content/25/2/284), (Retrieved 16th June 2016)
- Deveci, et al. 2008, Can the International Index of Erectile Function distinguish between organic and psychogenic erectile function? Pub MED.gov, (abstract available online at http://www.ncbi.nlm.nih.gov/pubmed/18336609), (Retrieved 2nd July 2016)
- Dhindsa et.al. 2004, Frequent Occurrence of Hypogonadotropic Hypogonadism in Type 2 Diabetes, (Abstract available online at http://press.endocrine.org/doi/full/10.1210/jc.2004-0804), (Retrieved 18th June 2016)
- Dhole et al. 2015, Guidelines on Male Hypogonadism, The European Association of Urology, (Available online at https://uroweb.org/wp-content/uploads/EAU-Guidelines-Male-Hypogonadism-2015.pdf), (Retrieved on 15th June 2016)

- Grossmann M. et al. 2008, Low testosterone levels are common and associated with insulin resistance in men with diabetes. Journal of Clinical Endocrinology and Metabolism 93:1834–1840
- Gulpinar et al. 2012. Help- seeking interval in erectile dysfunction: analysis of attitudes, beliefs and factors affecting treatment-seeking interval in Turkish men with previously untreated erectile dysfunction, Journal of Andrology: 33(4):624-628.
- Heufelder A. et al. 2009, Fifty-two-week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. Journal of Andrology, 30:726–733
- Inman et al.2009.A population-based, longitudinal study of erectile dysfunction and future coronary artery disease. Mayo Clinical Proceedings, 84(2):108–113.
- Kapoor D. et al. 2006, Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes, European Journal of Endocrinology, 154:899–906
- Kapoor D. et al. 2007. Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes: correlations with bioavailable testosterone and visceral adiposity, Diabetes Care, 30:911–917
- Lapauw B, Ouwens M, 't Hart LM, et al. Sex steroids affect triglyceride handling, glucose-dependent insulinotropic polypeptide, and insulin sensitivity: a 1-week randomized clinical trial in healthy young men. Diabetes Care 2010;33:1831–1833,(Available online at http://care.diabetesjournals.org/content/34/7/1669.full), (Retreived 16th June 2016)
- Lindau et al.2010. Sexuality among middle-aged and older adults with diagnosed and undiagnosed diabetes: a national, population-based study. Diabetes Care 2010; 33:2202–2210. (Available online at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2945161/), (Retrieved 16th June 2016)
- Lowry, F. 2010. NIH testosterone trial in older men halted due to increased cardiovascular events, Medscape, (Available online at http://www.medscape.com/viewarticle/790654), Retrieved 27th June 2016)
- Malkin et al.2004, The Effect of Testosterone Replacement on Endogenous Inflammatory Cytokines and Lipid Profiles in Hypogonadal Men, Endocrine Society. (Available online at http://press.endocrine.org/doi/full/10.1210/jc.2003-031069), Retrieved June 16th 2016)

- McBride et al.2016, Testosterone Deficiency in The Aging Male, Therapeutic Advances in Urology, (Available online at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4707424/), (Retrieved 28th June 2016)
- Monroe and Dobs, 2013. The effect of Androgens on Lipids, Current Opinion in Endocrinology, Diabetes and Obesity;20(2):132-9. (Abstract available online at http://www.ncbi.nlm.nih.gov/pubmed/23422242), (Retrieved 18th June 2016)
- (Muraleedharan,V. and Jones, T. 2010, Testosterone and the Metabolic Syndrome, Therapeutic Advances in Endocrinology and Metabolism, 1(5): 207–223.(Available online at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3474619/), (Retrieved 1st July 2016)
- Penson and Wessells, 2004 Erectile Dysfunction in Diabetic Patients, Diabetes Spectrum;17(4):225-230. (Available online at http://spectrum.diabetesjournals.org/content/17/4/225), (Retrieved 30th June 201
- Perry-Keen, D. 2014, Low Testosterone in Men, Australian Prescriber, 37:196-200, Available on line at (http://www.australianprescriber.com/magazine/37/6/196/200), (Retrieved 26th February 2015)
- Rhoden E. et al, 2002,The use of the simplified International Index of Erectile Function (IIEF-5) as a diagnostic tool to study the prevalence of erectile dysfunction. Int J Impot Res. 2002, 14: 245-250.
- Rhoden E. et al. 2005. Diabetes mellitus is associated with subnormal serum levels of free testosterone in men, Journal of the British Association of Urological Surgeons, 96:867–870
- Rosner W. et al. 2007, Position Statement: Utility, limitations, and pitfalls in measuring testosterone: An Endocrine Society position statement, Journal of Clinical Endocrinology and Metabolism, 92:405-13.
- Rosen et al. Erectile dysfunction in type 2 diabetic men: relationship to exercise fitness and cardiovascular risk factors in the Look AHEAD trial. Journal of Sexual Medicine 2009;6:1414–1422
- Rosner W. et al. 2007, Position Statement: Utility, limitations, and pitfalls in measuring testosterone: An Endocrine Society position statement, Journal of Clinical Endocrinology and Metabolism, 92:405-13.

- Skeldon et al. 2015, Erectile Dysfunction and Undiagnosed Diabetes, Hypertension, and Hypercholesterolemia, Annals of Family Medicine, vol. 13 no. 4 331-335, (Available online at http://www.annfammed.org/content/13/4/331.full), (Retrieved 20th June 2016)

- Traish et al. 2009. Testosterone and erectile function: from basic research to a new clinical paradigm for managing men with androgen insufficiency and erectile dysfunction. European Urology;52:54–70, (Available online at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2562639/), (Retrieved 18th June 2016)

- Tang et al.2014 Comparison of the simplified International Index of Erectile Function (IIEF-5) in patients of erectile dysfunction with different pathophysiologies, BMC Urology, (Available online at http://bmcurol.biomedcentral.com/articles/10.1186/1471-2490-14-52), (Retrieved 26th June 2016)

- The World Bank: Barbados. 2013 Report , (Available online at http://data.worldbank.org/country/barbados), Retrieved 29th June 2016)

- Wang et al. 2011, Low Testosterone Associated with Obesity and Metabolic Syndrome Contributes to Sexual Dysfunction and Cardiovascular Disease Risk in Men with Type 2 Diabetes , Diabetes Care, 34(7):1669-1675

- Zhang et al. 2014, Help-seeking behavior for erectile dysfunction: A clinic-based survey in China, Asian Journal of Andrology, Available online at (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3901871/), (Retrieved 3rd of February 2015)