What is the best biological parameter to predict erectile dysfunction in men aged >55 years with type 2 diabetes?

Straka A Raharinavalona¹, Nicolas Chevalier², Claude Gruel¹, André-Christian N'toutoum¹, Fritz-Line Vélayoudom Céphise¹,³*

¹Department of Endocrinology and Diabetology, University Hospital of Guadeloupe, Les Abymes, Guadeloupe, ²Department of Endocrinology, Diabetology, Reproduction, Hôpital de l'Archet, Centre Hospitalier Universitaire de Nice, Université Côte d'Azur, Inserm UMR U1065/UNS, Nice, and ³LAMIA EA-4540, University of Antilles, Guadeloupe, France

Keywords
Bioavailable testosterone, Erectile dysfunction, Total testosterone

*Correspondence
Fritz-Line Vélayoudom Céphise
Tel.: +33-5-9089-1300
Fax: +33-5-9089-1302
E-mail address: fritz-line.velayoudom@univ-antilles.fr

J Diabetes Investig 2020; 11: 170–173
doi: 10.1111/jdi.13089

INTRODUCTION
Erectile dysfunction (ED) is defined as an inability to have a sufficient erection for satisfactory sexual intercourse¹. The frequency of ED is higher in men with type 2 diabetes compared with those without diabetes². ED is usually associated with hypogonadism (HG) defined by low total testosterone (TT) levels³,⁴. However, interpretation of TT is difficult in men aged >55 years, particularly in the case of type 2 diabetes. Some have proposed using bioavailable testosterone (BioT) or the free testosterone index (FTI) instead⁵, but no study could confirm their usefulness. We aimed to evaluate the relationship between ED and these three biological parameters in order to detect the best biological tool to predict ED in this population. Our findings could affect the clinical practice of physicians in the management of ED.

METHODS
We carried out a cross-sectional study including all men aged >55 years with type 2 diabetes, after oral agreement, in the Department of Diabetology of the University Hospital of Guadeloupe. Patients with renal or prostate disease and cognitive disorders were excluded.

Clinical data
ED was evaluated with the International Index of Erectile Function 15-item (IIEF-15) survey. The diagnosis of ED was confirmed when the IIEF-15 score was <26⁶. Clinical parameters, including anthropometric data, were included.

Biological assessments
Serum TT levels were measured using an electrochemiluminescence method. HG was defined as serum TT <10.4 nmol/L. According to the Vermeulen formula, BioT was obtained from a calculation using sex hormone-binding globulin, albumin and TT⁷. Low BioT was defined by plasmatic levels <3.87 nmol/L. When the TT levels were between 8 and 10.4 nmol/L, the FTI was calculated. We also collected the levels of fasting blood glucose, glycated hemoglobin, lipids, 25(OH) vitamin D and high-sensitivity C-reactive protein (hs-CRP).

Statistical analysis
Data are presented as the mean ± standard deviation for continuous variables, and percentages (numbers) for categorical
variables. Data were analyzed using the χ²-test and t-test, Pearson’s and Spearman’s correlation, and the odds ratio with a 95% confidence interval. Results were considered significant when \( P < 0.05 \) (two-sided).

After approval by the local ethics committee, all men received a detailed note before they gave their oral informed consent. No men objected to the study.

In respect to the national legislation about data protection, a declaration of conformity has been made to the National Data Information and Freedom Commission.

**RESULTS**

We analyzed the data collected from 155 men aged >55 years with type 2 diabetes, included during 8 months in 2017. The characteristics of the population are summarized in Table 1. ED was self-reported by 67.6% of the men, while its frequency was 78.7% using the IIEF-15 survey. HG was found in 34.8% of patients.

Comparison of clinical and biological parameters between men with or without ED is reported in Table 1. The sensitivity and specificity of TT for the diagnosis of ED were 89.66% and 29.27%, respectively.

BioT levels were low in 25.9% of patients. We observed a positive correlation between TT and BioT \( (P = 0.001) \), and an inverse correlation between TT levels and ED \( (P = 0.011) \). This inverse correlation was not observed for BioT and FTI.

After univariate analysis, TT and BioT were significantly associated with ED score (odds ratio [OR] 0.91, 95% confidence interval [CI] 0.84–0.98, \( P = 0.01 \)) and OR 0.73, 95% CI 0.58–0.93, \( P = 0.01 \)). No association was found between FTI and ED \( (P = 0.75) \). We carried out a multivariate analysis with adjustment for age, body mass index, tobacco, alcohol and duration of type 2 diabetes; we found that only TT was associated with ED \( (OR = 0.92, 95\% CI 0.84–1.00, P = 0.06) \). However, after additional adjustment for BioT, vitamin D and hs-CRP, only hs-CRP levels were associated with ED \( (OR = 1.71, 95\% CI 1.00–2.89, P = 0.046) \).

**DISCUSSION**

According to our knowledge, this is the first time that the three forms of testosterone evaluation are analyzed together as predictive factors of ED.

The subject of sexuality remains difficult to address, even in the field of health, which can explain why ED is not usually evaluated in men with type 2 diabetes, despite clear recommendations. According to a recent meta-analysis, the prevalence of ED in diabetes patients was 52.5%, lower than our findings of 78.7% using the IIEF-15 score, targeting men aged >55 years. As the frequency of self-reported ED was 67.6% in our cohort, we can assume that both physicians and patients themselves underestimated ED.

| Characteristics                      | All patients | Men with ED | Men without ED | P-value |
|--------------------------------------|-------------|-------------|----------------|---------|
| Age (years)                          | 64 ± 7      | 63 ± 6      | 61 ± 5         | 0.18    |
| Diabetes duration (months)           | 97.5 ± 84   | 104.2 ± 55.8| 81.7 ± 79.5    | 0.36    |
| High blood pressure (%)              | 26.5%       | 58%         | 53%            | 0.77    |
| Dyslipidemia (%)                     | 19.4%       | 40%         | 39.5%          | 0.39    |
| Body mass index (kg/m²)              | 27.2 ± 4.3  | 27.7 ± 4.5  | 25.5 ± 3.5     | 0.079   |
| Waist circumference (cm)             | 100.9 ± 13.3| 102.4 ± 13.7| 96.9 ± 10.6    | 0.17    |
| Penile size (cm)                     | 87. ± 2.6   | 82 ± 2.3    | 109 ± 2.5      | 0.09    |
| Volume of testis (mL)                | 14.7 ± 5.1  | 13.9 ± 4.6  | 165 ± 6.1      | 0.0001  |
| IIEF-15 score                        | 16.4 ± 9.2  | 13.3 ± 7.8  | 279 ± 12       | 0.0001  |
| Fasting blood glucose (mg/dL)        | 148 ± 70    | 140 ± 64    | 141 ± 75       | 0.97    |
| eGFR (mL/min/1.73 m²)                | 82.7 ± 20.4 | 90.1 ± 21.07| 90.8 ± 13.4    | 0.90    |
| AER (mg/day)                         | 37.18 ± 66.5| 32.67 ± 69.2| 106.3 ± 10.65  | 0.04    |
| HbA1c (%)                            | 9.1 ± 3.1   | 10.1 ± 3.2  | 9.6 ± 3.6      | 0.59    |
| 25(OH) vitamin D (nmol/L)            | 86.5 ± 33.96| 82.35 ± 33.33| 97.13 ± 34.33 | 0.14    |
| SHBG (nmol/L)                        | 448 ± 249   | 407 ± 21.9  | 527 ± 38.9     | 0.12    |
| Total testosterone (nmol/L)          | 13.1 ± 6.9  | 12.2 ± 7.4  | 18.8 ± 9.6     | 0.006   |
| Bioavailable testosterone (nmol/L)   | 5.3 ± 2.3   | 4.9 ± 2.6   | 7.2 ± 2.7      | 0.004   |
| Free testosterone index              | 34.4 ± 9.1  | 36.2 ± 8.3  | 33.6 ± 8.1     | 0.77    |
| Hypogonadism (%)                     | 34.8%       | 47.3%       | 20%            | 0.078   |
| hs-CRP use (mg/L)                    | 5.76 ± 10.87| 7.56 ± 12.06| 1.69 ± 1.5     | 0.001   |

Data are presented as the mean ± standard deviation for continuous variables and percentages (numbers) for categorical variables. Results were considered significant when \( P < 0.05 \). The significant values are highlighted in bold. AER, albumin excretion rate; ED, erectile dysfunction; IIEF-15, International Index of Erectile Function 15-item version questionnaire; eGFR, estimated glomerular filtration rate obtained by Modification of Diet in Renal Disease Study method; HbA1c, glycated hemoglobin; SHBG, sex hormone-binding globulin.
Although the IIEF-15 is a simple and reliable tool for ED diagnosis, it remains difficult to determine the pathophysiological origin of ED. ED observed in type 2 diabetes can result from both neuropathy and distal arteriopathy\textsuperscript{9,10}. However, diabetes itself is associated with HG defined by low TT levels. Furthermore, it is well known that TT decreases with age, particularly after the age of 55 years and, finally, its measurement is only recommended in the case of symptoms\textsuperscript{3}.

In the present cohort, we observed 34.8\% of HG, defined as a serum level of TT under 10.4 nmol/L. Our levels of TT were closer to those described in previous studies\textsuperscript{10,11}. However, the frequency of HG was noticeably higher\textsuperscript{11}. Considering the ED statute as the main outcome, we reported a good sensitivity, but a very low specificity of TT in our population, which highlights the lack of clinical usefulness of this biomarker.

The use of other markers of HG, such as BioT or FTI, has so far proposed been, but has not been confirmed yet. Furthermore, in a recent study carried out on a general population, independently of TT, higher sex hormone-binding globulin was associated with either subjective or objective androgen deficiency features\textsuperscript{12}. This remains to be confirmed in patients with type 2 diabetes.

The significant correlation between TT and BioT is relevant, but both parameters are not associated with ED in the same way. We confirmed here that FTI is not useful.

We highlighted the role of hs-CRP as a possible good predictive marker of ED. The role of hs-CRP on metabolic syndrome, associated or not with low TT, is well known, particularly in elderly healthy men aged \textgreater 75 years, but studies targeting men with type 2 diabetes are lacking\textsuperscript{13}. hs-CRP is clearly known as a biomarker of the cardiovascular risk of people with type 2 diabetes or polycystic ovary syndrome. The predictive role of hs-CRP for ED was previously described in obese people without type 2 diabetes\textsuperscript{14}. However, to our knowledge, it is the first time that its predictive role for ED in men aged \textgreater 55 years with type 2 diabetes has been described and compared with TT, BioT and FTI. It has been previously reported that hs-CRP levels were associated with a moderate-to-high cardiovascular risk in non-diabetic men with moderate-to-severe ED\textsuperscript{15}. Another study reported that hs-CRP levels were higher in diabetes patients with ED compared with those without ED, but the present study did not target the specific population of men aged \textgreater 55 years, and included younger men without measurement of the sex steroids levels\textsuperscript{16}.

The impact of the present finding is very important, as a previous study reported that ED could be the first clinical sign of endothelial dysfunction and a clinical marker of cardiovascular diseases. Finally, our results could change the clinical management of men with diabetes, particularly for the screening of cardiovascular risk factors\textsuperscript{17}.

**Conclusion**

BioT or FTI are not good markers to evaluate ED in men aged \textgreater 55 years with type 2 diabetes. TT lacks specificity in this studied population. However, unexpectedly, we found that hs-CRP could have a potential role as a predictive marker of ED.

**ACKNOWLEDGMENT**

No external funding source was used.

**DISCLOSURE**

The authors declare no conflict of interest.

**REFERENCES**

1. NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. JAMA 1993; 270: 83–90.
2. Grant PS, Lipscomb D. How often do we ask about erectile dysfunction in the diabetes review clinic? Development of a neuropathy screening tool. Acta Diabetol 2009; 46: 285–290.
3. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2018; 103: 1715–1744.
4. Chung E, Al-Bermani OS, Fowler RP, et al. Testosterone deficiency and erectile dysfunction: a practical approach to diagnosis and management. J Endocrinol Diabetes Obes 2013; 1: 1012.
5. Kapoor D, Clarke S, Channer KS, et al. Erectile dysfunction is associated with low bioactive testosterone levels and visceral adiposity in men with type 2 diabetes. Int J Androl 2007; 30: 500–507.
6. Rosen RC, Riley A, Wagner G, et al. The International Index of Erectile Function (IIEF): a multidimensional scale for assessment erectile dysfunction. Urology 1997; 49: 822–830.
7. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab 1999; 84: 3666–3672.
8. Koudrat Y, Pizzol D, Cosco T, et al. High prevalence of erectile dysfunction in diabetes: a systematic review and meta-analysis of 145 studies. Diabet Med 2017; 34: 1185–1192.
9. Maiorino Ml, Bellastella G, Esposito K. Diabetes and sexual dysfunction: current perspectives. Diabetes Metab Syndr Obes 2014; 7: 95–105.
10. Velayoudom Céphise FL, Foucan L, Larïfia L, et al. Relationship between testosterone and sex hormone binding globulin concentrations with cardiometabolic parameters and macrovascular disease in Afro-Caribbean men with Type 2. Diabetes Endocrinol Metab Syndr 2015; 4: 162.
11. Corona G, Mannucci E, Petrone L, et al. Association of hypogonadism and type II diabetes in men attending an outpatient erectile dysfunction clinic. Int J Impot Res 2006; 18: 190–197.
12. Rastrelli G, Corona G, Cipriani S, et al. Sex hormone-binding globulin is associated with androgen deficiency features independently of total testosterone. Clin Endocrinol (Oxf) 2018; 88: 556–564.
13. Chrysohou C, Panagiotakos D, Pitsavos C, et al. Low total testosterone levels are associated with the metabolic
syndrome in elderly men: the role of body weight, lipids, insulin resistance, and inflammation; the Ikaria study. Rev Diabet Stud 2013; 10: 27–38.

14. Shi MD, Chao JK, Ma MC, et al. Factors associated with sex hormones and erectile dysfunction in male Taiwanese participants with obesity. J Sex Med 2014; 11: 230–239.

15. Ferrandis-Cortes C, Martínez-Jabaloyas JM, Díez-Calzadilla NA, et al. Cardiovascular risk assessment using high-sensitivity C-reactive protein in patients with erectile dysfunction. Urol Int 2013; 91: 187–191.

16. Lee JW, Park HJ, Park NC. Serum high-sensitivity C-reactive protein levels and response to 5 mg tadalafil once daily in patients with erectile dysfunction and diabetes. Korean J Urol 2013; 54: 858–864.

17. Yao F, Liu L, Zhang Y, et al. Erectile dysfunction may be the first clinical sign of insulin resistance and endothelial dysfunction in young men. Clin Res Cardiol 2013; 102: 645–651.