Digestive and Liver Disease 48 (2016) 1155–1161

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

Low testosterone in non-responsive coeliac disease: A case series, case–control study with comparisons to the National Health and Nutrition Examination Survey

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ARTICLE INFO

Article history:
Received 24 April 2016
Accepted 6 June 2016
Available online 18 June 2016

Keywords:
Coeliac disease
Fatigue
Non responsive coeliac disease
Osteoporosis
Testosterone

ABSTRACT

Background: Adults with coeliac disease (CD) often report persistent fatigue, even when CD appears well controlled for unknown reasons.
Aims: To evaluate common indications for testosterone panel (TP) testing and prevalence of low testosterone (T) in CD.
Methods: In our case series, we determined common indications for checking TP in CD. Next, we conducted a case–control study to compare TP in CD vs. healthy controls (HC). We compared mean total T (TT), free T (FT) based on serologic, histologic disease activity. Finally, we assessed TT in tissue transglutaminase (tTG)+ vs. tTG− subjects and CD vs. HC obtained from the National Health and Nutrition Examination Survey (NHANES).
Results: 53 coeliac males had TP tested. Common indications included osteoporosis and fatigue. Low FT was observed in 7/13 men with osteoporosis and 5/6 with fatigue. In our case–control study ($n = 26$ each), there was no difference in mean TT or FT between CD vs. HC, tTG+ vs tTG− or Marsh 0 vs. Marsh 3 groups. NHANES data showed no difference in mean TT between tTG+ vs tTG− ($n = 16$ each) or CD vs. HC subjects ($n = 5$ each).
Conclusions: Low T occurs in CD patients at a similar rate as the general population. Common presentations of low T may mimic non-responsive CD symptoms.

1. Introduction

Adults with coeliac disease (CD) commonly present with vague symptoms such as fatigue, malaise and depression. A subsect of patients have ongoing symptoms despite adoption of a gluten free diet and these symptoms may affect long term adherence to a gluten free diet (GFD) in addition to established factors such as cost and perception of effectiveness of a gluten free diet [1–4]. Often these subtle and non-specific symptoms are attributed to coexisting rheumatological conditions including fibromyalgia [5] and to nutritional deficiencies such as carnitine, iron, vitamin B complex, and vitamin D, that are commonly seen in both treated and untreated CD [6–12]. These deficiencies may also occur in patients on a GFD due to inherent deficiencies of a GFD [12,13]. Although, this has not been directly proven, intuitively other autoimmune endocrine phenomenon such as hypothyroidism may also contribute to the persistent symptoms in some cases [14–17].

While gastrointestinal symptoms of CD often respond promptly to the GFD, extra-intestinal symptoms including fatigue may be persistent and lead to further evaluation under the umbrella of non-responsive coeliac disease [18,19]. Observations made in early literature have demonstrated elevated total testosterone (TT), elevated free testosterone (FT), elevated luteinizing hormone (LH) and diminished levels of 5-dihydrotestosterone (5-DHT) in CD [20,21]. Several potential hypotheses to explain these observations have been postulated such as androgen insensitivity or an inability to convert FT to DHT due to loss of intestinal 5-alpha reductase, though these have not been definitive [20–24]. Green et al. demonstrated reversible androgen sensitivity with mucosal recovery in coeliac

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http://dx.doi.org/10.1016/j.dld.2016.06.006
1590-8658/

subjects on a gluten free diet [21]. An androgen resistance pattern of hypogonadism was demonstrated by Farthing et al. in coeliac men with elevated TT, FT, LH and low dihydro-testosterone (the active form of testosterone) in untreated coeliac subjects compared to other inflammatory conditions including Crohn's disease and rheumatoid arthritis [23]. Gluten peptides are also known to have opioid exorphin-like activity and may contribute to hypogonadism by suppressing production of the pituitary hormones LH and follicle stimulating hormone (FSH) [25]. Another mechanism that may contribute to hypogonadism and delayed puberty in adolescent males is decreased DHEA-S (dihydro-epiandrosterone sulfate) levels, which is seen in patients with adrenal insufficiency [26]. Coeliac patients have also been shown to have autoantibodies to several endocrine glands like the pancreas, thyroid and possibly the adrenal glands [26]. Also, it has been shown that women with untreated coeliac disease have shorter fertile periods, late menarche, earlier menopause compared to treated coeliac women and healthy controls in a study [27]. In the same study untreated coeliac women demonstrated greater incidence of hot flashes, muscle and joint problems and irritability compared to treated coeliac patients and healthy controls [27]. We may extrapolate that a similar phenomenon exists in men. Although these studies support the concept of the potential for low testosterone to be a significant issue in men with CD, the clinical relevance of these hormonal abnormalities in contemporary practice is unclear. The goal of our study was to explore the epidemiology and clinical relevance of low testosterone in adult men with coeliac disease.

2. Methods

This work was conducted at Beth Israel Deaconess Medical Center in three phases, described below and in Fig. 1A and B. This study was approved by the institutional review board at Beth Israel Deaconess Medical Center, Boston, MA.

2.1. Case series

We retrospectively identified all adult male coeliac patients from July 2005 to July 2015 from our database. We ensured that these patients had a definitive diagnosis of coeliac disease by documenting positive serology and Marsh 3 lesions on biopsy. This list was cross-referenced against laboratory results to identify all men with coeliac disease who had the testosterone panel checked during this time period. All records were then reviewed to determine the indications for checking testosterone levels and response to clinical therapy if initiated. We further classified these subjects into low/normal (TT) and low/normal (FT) groups. Low TT was defined a TT <280 ng/dL based on the assay used at Beth Israel Deaconess Medical Center. Electro-chemiluminescence immunoassay (ECLIA) was used for determination of TT and sex hormone binding globulin

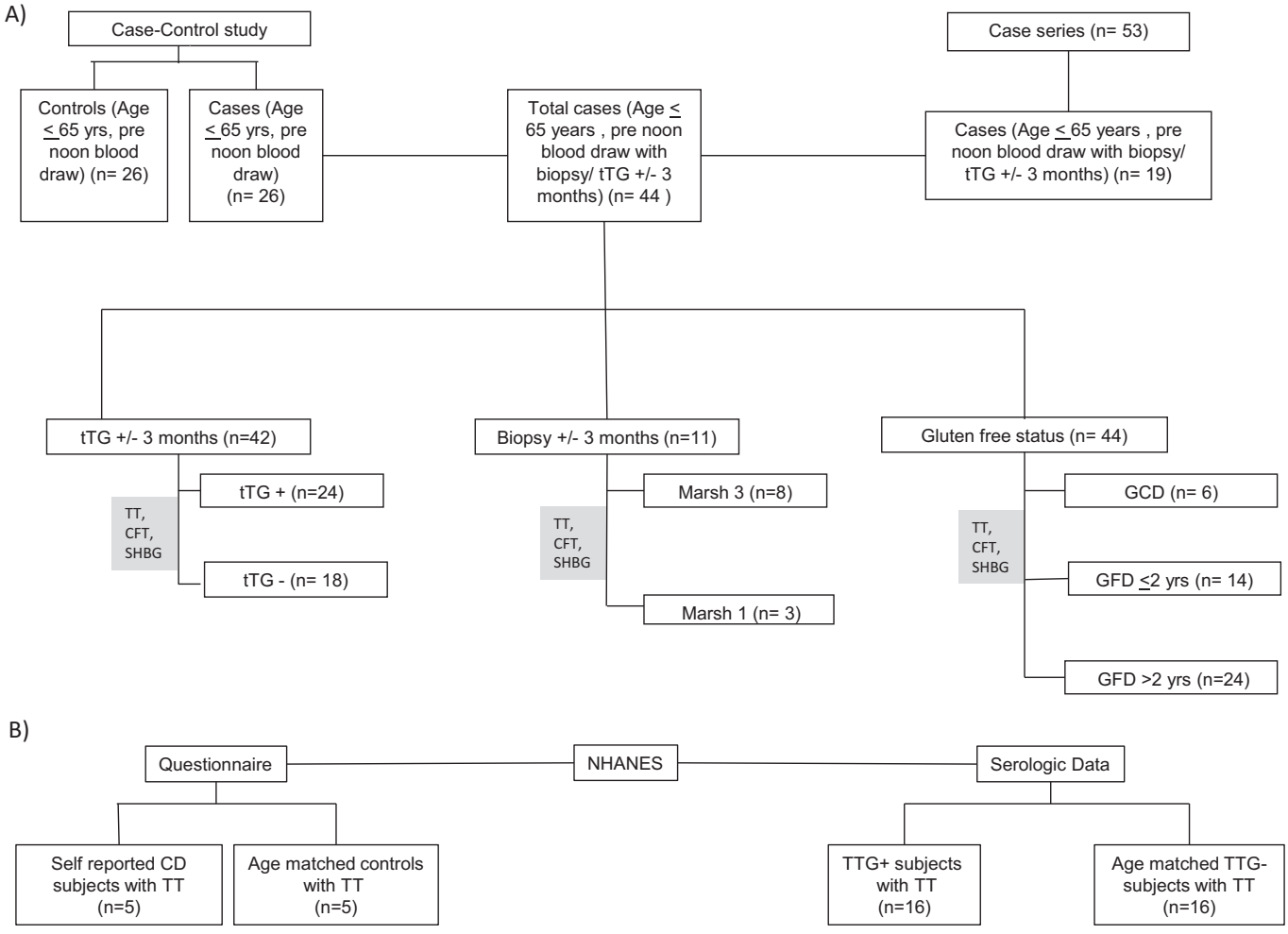

Fig. 1. (A) Flow diagram showing evolution of case series, case–control study and subgroup analysis based on histology, serology and gluten status of diet. (B) Flow diagram showing evolution of analysis in the National Health and Nutrition Examination Survey (NHANES). *Abbreviations*: GCD, gluten containing diet; GFD, gluten free diet; tTG, anti-tissue transglutaminase IgA; TT, total testosterone; CFT, calculated free testosterone; SHBG, sex hormone binding globulin. *Legend*: Marsh 1: Biopsy showing intraepithelial lymphocytes Marsh 3: Biopsy showing intraepithelial lymphocytes with crypt hyperplasia and villous atrophy.