

Do Male Sex Hormones Protect From Irritable Bowel Syndrome?

L. A. Houghton, Ph.D., N. A. Jackson, B.Sc., P. J. Whorwell, M.D., F.R.C.P., and J. Morris, M.Sc.
Departments of Medicine and Medical Statistics, University Hospital of South Manchester, Manchester, United Kingdom

OBJECTIVE: Irritable bowel syndrome (IBS) is more common in women and it is frequently assumed that being female may predispose to the development of this disorder. Alternatively, being male could offer some degree of protection and if so, this might be mediated by testosterone. The aim of this study was to assess whether male patients with IBS have lower levels of testosterone and related gonadotrophins than their unaffected counterparts and if this relates to rectal sensitivity.

METHODS: Fifty secondary care, male outpatients with IBS (aged 19–71 yr) were compared with 25 controls (aged 22–67 yr). Each subject had serum testosterone, free testosterone, sex hormone-binding globulin, follicle stimulating hormone, and luteinizing hormone (LH) measured, together with rectal sensitivity to balloon distension. Anxiety and depression were also assessed.

RESULTS: The only difference in the hormone levels between patients and controls that reached statistical significance was the lower value for LH in the IBS patients ($p = 0.014$). Although patients were more anxious and depressed than the controls ($p < 0.001$), this could not solely account for the reduced level of LH, as adjusting for these (analysis of variance) still tended to show that LH values were lower in men with rather than without IBS [$F(1,70) = 2.74$; $p = 0.10$]. Men with IBS were more sensitive to balloon distension of the rectum, with the distension volumes required for “urgency” ($p < 0.001$) and “discomfort” ($p = 0.001$) significantly lower than controls. Paradoxically, the patient’s sensory thresholds negatively correlated with levels of testosterone ($p < 0.05$) and free testosterone ($p < 0.002$), and positively with levels of sex hormone-binding globulin ($p < 0.05$). Finally, there was a tendency for IBS symptomatology to be inversely related to testosterone levels ($p = 0.15$).

CONCLUSIONS: These results support the need for further exploration of the role of male sex hormones in the pathophysiology of IBS. (*Am J Gastroenterol* 2000;95:2296–2300. © 2000 by Am. Coll. of Gastroenterology)

INTRODUCTION

Irritable bowel syndrome (IBS) appears to be more common in women (1) and a variety of reasons for this observation

has been suggested ranging from psychosocial through to physiological factors. However, it seems unlikely that cultural/economic factors, which influence health seeking behavior, are the sole cause for this difference, as there appears to be a similar female-to-male ratio in patients who do not seek medical help (2, 3). Possible physiological mechanisms include differences in both the sensory and motor function of the gut. Studies have shown that healthy women pass firmer (4) and lower weight (5) stools than men. This may partly be attributable to the delayed colonic transit observed in women (6), which appears to be related to delayed transit through the ascending and transverse colon rather than the descending colon (7). Gender differences in the absorptive capacity of the intestine (8), as well as differences in ano-rectal motor function (9, 10) have also been reported.

Sensory differences have been noted in most regions of the GI tract, with healthy women exhibiting lower pain thresholds to balloon distension than men (9–11). In patients with IBS, this female–male difference appears to be shifted more toward abnormal levels (12, 13). Furthermore, the intra- (between) subject variation in sensory threshold appears to be wider in men than women (12, 13), and this coupled with their reduced sensitivity may suggest that they are less susceptible to sensitizing events. This is supported by the observations that female volunteers show a greater tendency to develop rectal sensitivity after experimentally induced diarrhea (14) and that women are more likely to develop IBS after an episode of dysentery (15).

These observations may be related to the hormonal environment associated with being a woman, as menstruation is associated with looser stools (5, 16), the luteal phase with delayed transit and harder stools (5, 17), and pregnancy with increased small bowel absorption (18). Furthermore, recently we have shown that although rectal sensitivity does not change throughout the menstrual cycle in healthy women (19), it does seem to vary in patients with IBS (20), suggesting that IBS patients may respond differently to fluctuations in sex hormones than healthy subjects and that female sex hormones may have a role in the etiology of IBS. However, the opposite view that men might be protected from IBS in some way, and that this may be mediated as a result of their sex hormones has not attracted so much attention. If this were the case, it might be speculated that

men with IBS could have a slightly lower testosterone levels than their unaffected counterparts. There is some evidence from animal studies to suggest that endogenous androgens may have an analgesic role, as males seem to require less morphine after induction of visceral pain (intraperitoneal injection of saline) than females (21).

Therefore, it was the purpose of this study to assess the sex hormone status of male subjects with and without IBS and correlate any differences found with rectal sensitivity.

MATERIALS AND METHODS

Subjects

Studies were carried out in 50 male patients with IBS (aged 19–71 yr; mean, 42.6 yr) and 25 healthy men (aged 22–67 yr; mean, 36.0 yr; $p = 0.03$). All patients were recruited from the outpatient department (secondary care patients) of the University Hospital of South Manchester and had to conform to the Rome Criteria (22). In addition, no patient had coexistent disease and had to have normal hematology, biochemistry, and sigmoidoscopy and either a normal barium enema or colonoscopy if aged more than 40 yr. Healthy controls were recruited by advertisement and IBS was excluded in these subjects. All subjects weighed within the permitted range for their height and frame size and were studied in the fasting state, at the same time of day, having been instructed to refrain from taking medication, smoking, drinking alcohol, or doing strenuous activity in the previous 48 h.

All subjects gave informed consent and the study was approved by the local Ethical Committee.

Experimental Protocol

On the day of study, subjects were placed in the left lateral position and a multilumen polyvinyl catheter was inserted into the rectum such that two side holes were in the rectum (4.5 and 15.0 cm from the anal verge) and three side holes in the anal sphincter (0.5, 1.0, 2.0 cm from the anal verge). Each side hole was perfused with distilled water at a rate of 0.2 ml/min (Arndorfer Medical Specialities Inc, Greendale, WI) and connected by water-filled transducers to a polygraph recorder and visual display unit (Synectics Medical, Stockholm, Sweden). A 6-cm length of distensible latex tubing was tied to the catheter between 5 and 11 cm from the anal verge and used to distend the rectum. The pressure within the rectal balloon was monitored using a water-filled nonperfused channel sited at 8 cm from the anal verge. After at least a 15-min basal period, the rectal balloon was serially inflated with air at 10, 20, 40, 60, 80, and 100 ml, and then in 25-ml increments until the subject experienced discomfort. Inflations were maintained for 1 min, and were separated by periods of at least 1 min in which the balloon was totally deflated. Throughout the study, the subjects were asked to mark on a standard proforma the nature of any sensation felt (*e.g.*, desire to defecate, urgency, and discomfort) having been previously informed of the nature of the

sensations that they might be expected to experience. All subjects were blinded to the onset of distension throughout the study.

Simple symptomatological data were collected from the IBS patients in terms of the severity of their abdominal pain and general well-being on the day of study (visual analog scales). In addition, each patient completed the Hospital Anxiety and Depression questionnaire (23).

Ten milliliters of venous blood was then taken from the patient, allowed to clot for 30 min and then spun at 2200 revolutions/min for 10 min (MSE Centaur 2 centrifuge, Sanyo Gallekamp PLC, Loughborough, UK). The serum obtained was then frozen at -20°C and stored until the end of the study, so that all assays could be done in one batch at the Regional Hormonal Laboratory. Luteinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone were run on an automated chemiluminescence system 180 instrument (Chiron Diagnostics Ltd, Halstead, UK). LH and FSH are two-site (sandwich) chemiluminometric immunoassays, whereas testosterone is a competitive chemiluminescent immunoassay. Sex hormone-binding globulin (SHBG) was run on an Immulite instrument (Euro/DPC Ltd, Llanberis, UK) and is a two-site chemiluminescent immunoassay.

Analysis of Data

The following measurements were derived for the study:

- Serum levels of testosterone, FSH, LH, and SHBG. The level of free testosterone was calculated from the following equation: (Serum testosterone level/Serum SHBG level) \times 100.
- The lowest balloon volumes required to induce the sensations of stool (or desire to defecate), urgency, and discomfort.
- The steady-state pressure in the rectal balloon at each distending volume and the rectal compliance (calculated from the volume-to-pressure relationship at 100 ml of distension).
- The rectal motility index during distension calculated by summing the area under the rectal pressure profiles at 4.5 and 15 cm from the anal verge.
- The basal anal pressure.
- The lowest distending volume required to initiate internal anal sphincter relaxation and to cause relaxation sustained throughout the distension.
- Scores for levels of anxiety and depression from the Hospital Anxiety and Depression questionnaire.

Statistical Analysis

Analyses of covariance (adjusting for age differences and anxiety/depression as appropriate) were used to assess differences in the various parameters between men with and without IBS. All parameters required a \log_e transformation before statistical analysis to produce an adequate approximation to a normal distribution. Relationships between var-

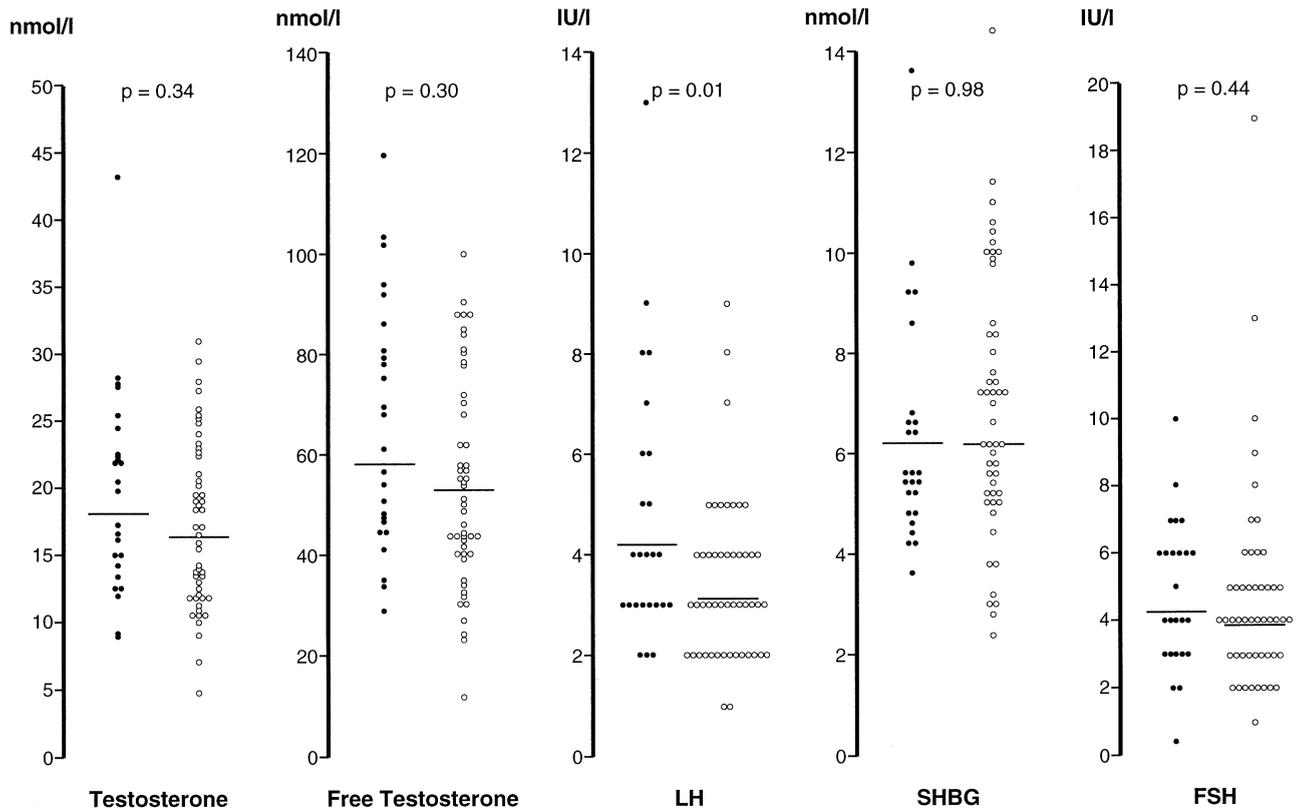


Figure 1. Serum levels of sex hormones in men with (○) and without (●) irritable bowel syndrome. Bars represent geometric mean corrected for age.

ious parameters were quantified using Pearson's or Spearman's correlations as appropriate.

RESULTS

Hormone Levels

As can be seen in Figure 1, the only difference between patients and controls that reached statistical significance was the lower LH values observed in the IBS patients ($p = 0.014$).

Anorectal Parameters

Male patients with IBS experienced the rectal sensations of urgency (IBS patients, geometric mean [range]: 51 ml [10–225 ml] vs controls: 88 ml [40–150 ml]; $p = 0.001$) and discomfort (86 ml [20–275 ml] vs 134 ml [60–225 ml]; $p < 0.001$) at significantly lower distension volumes than healthy men. However, the distension volume required to induce the sensation of stool (24 ml [10–150 ml] vs 31 ml [10–80 ml]; $p = 0.20$) was not significantly different between the patients and controls.

Furthermore, although the volume required to induce sustained internal anal sphincter relaxation was significantly lower in the patients compared with the controls (mean (range) 102 ml [20–250 ml] vs 142 ml (60–225 ml); $p = 0.01$), the volume required to induce the initial anal sphincter relaxation was not significantly different between the two groups (geometric mean (range) 12 ml [10–20 ml] vs

11 ml [10–20 ml]; $p = 0.09$). Likewise, there were no significant differences in either the rectal compliance (mean (range) 7.8 ml/cm H₂O [2.7–16.1 ml/cm H₂O] vs 7.8 ml/cm H₂O [3.8–14.3 ml/cm H₂O]; $p = 0.94$), motility index (geometric mean (range) 632 [186–6262] vs 616 [170–3490]; $p = 0.92$), or basal anal pressure (86 cm H₂O [51–144 cm H₂O] vs 85 cm H₂O [63–118 cm H₂O]; $p = 0.80$) between the two groups.

Relationship Between Hormone Levels and Anxiety/Depression

Patients were both more anxious (patients, 7.8 [1–19] vs controls, 4.8 [1–10]; $p = 0.002$) and depressed (4.3 [1–20] vs 2.2 [1–9], $p = 0.002$) than the controls. Furthermore, LH levels appeared to be slightly more influenced by anxiety (from analysis of variance table; percentage variation in log_e LH values between patients and controls explained by anxiety is 7.5%) than either IBS status (*i.e.*, subjects with or without IBS: 3.5%), depression (0.1%), or the age of the subject (0.009%). However, despite these observations, the reduced levels of LH seen in the patients could not be solely explained by these factors, as adjusting for all of them (analysis of variance) still tended to show that LH values were lower in the patients than in the controls (adjusted geometric means [95% confidence interval], 3.18 IU/L [2.77–3.65 IU/L] vs 3.95 IU/L [3.22–4.85 IU/L]; $F(1, 70) = 2.74$; $p = 0.10$).

Relationship Between Sensory Threshold and Anxiety/Depression

There was no relationship between any of the sensory thresholds measured and either anxiety or depression.

Relationship Between Sensory Threshold and Hormone Levels

There was an inverse relationship in the patients between the level of serum testosterone and the sensory threshold for urgency ($\rho = -0.32$; $p = 0.03$) and discomfort ($\rho = -0.29$; $p = 0.04$) and between the level of free testosterone and sensory threshold for stool ($\rho = -0.49$; $p = 0.001$), urgency ($\rho = -0.53$; $p < 0.001$), and discomfort ($\rho = -0.47$; $p = 0.001$). Conversely, there was a direct relationship in the patients between the level of plasma SHBG and the sensory thresholds for stool ($\rho = 0.4$; $p = 0.006$) and urgency ($\rho = 0.31$; $p = 0.039$), but not discomfort ($\rho = 0.17$; $p = 0.24$). There were no other correlation in the patients between the levels of serum LH or FSH and any sensory threshold or between the hormone levels and sensory thresholds in the controls.

Relationship Between Symptomatology and Hormone Levels/Sensory Thresholds

There was a tendency in the patients for the level of serum testosterone to inversely correlate with the level of pain ($\rho = -0.21$; $p = 0.15$) and general well-being ($\rho = -0.20$; $p = 0.18$). However, there was no correlation between either pain or general well-being and any of the other hormones measured in the patients. Likewise, there was no correlation between symptomatology and sensory threshold.

DISCUSSION

The results of this study support in part the concept that sex hormonal status may play a role in the relatively lower prevalence of IBS in men.

There appears to be a clearcut difference in the levels of LH between men with and without IBS. The relatively low levels of LH in men with IBS is of particular interest as it would suggest some dysfunction of the hypothalamopituitary axis, which would neatly fit with some of the current pathophysiological concepts of stress and IBS. Furthermore, these changes in LH might be expected to result in small reductions in serum testosterone, and if testosterone is protective in men, may also lead to greater symptom severity. However, our results for these latter two parameters failed to reach statistical significance and much larger groups of men would have to be studied. Given the relative paucity of IBS in men it would probably be necessary to undertake a multicenter study to answer this particular question.

Unlike the sex-related hormones of women, those of men do not undergo the cyclical changes seen in the premenopausal subject or the abrupt changes seen at the time of menopause, but there is a tendency for testosterone to decline with age (24, 25). The IBS group in this study was

slightly older than the controls and although this was corrected for in the statistical analysis, the IBS group should have had higher rather than lower levels of LH and this actually strengthens the validity of our observations on LH. Other factors such as diet (26, 27), obesity (28, 29), alcohol intake (30, 31), time of day (25), season (32, 33), and stress, whether physical or psychological (*i.e.*, anxiety, depression) (34–36), have all been reported as being able to affect levels of testosterone. All these factors were controlled for as far as possible in this study, with the exception of stress, anxiety, and depression, where the IBS patients scored significantly higher on the Hospital Anxiety and Depression questionnaire. Moreover, anxiety did seem to have a slightly greater influence on LH levels (explaining 7.5% of variation in data between patients and controls) than either depression (0.1%) or IBS status (3.5%). However, after correcting for these factors in the statistical analysis, LH values still tended to be lower in the IBS patients compared with the healthy volunteers.

Stress is well-known to effect hypothalamopituitary function and might explain the changes in LH observed in this study. This obviously raises the possibility that any changes observed in male sex hormones may be an epiphenomena reflecting pituitary dysfunction rather than being indicative of a role for these hormones in the pathophysiology of IBS.

With respect to LH, it has been reported that the use of the gonadotropin-releasing hormone analog leuprolide acetate, which dramatically reduces levels of LH, may lead to improvement in some cases of chronic abdominal pain in women (37, 38). This would lend some support to the hypothesis that LH may have a contributory role in the pathophysiology of IBS by virtue of the fact that it stimulates hormones that might be detrimental in women (*e.g.*, estrogen, progesterone) and protective in men (*e.g.*, testosterone).

Rectal hypersensitivity is a frequent observation in patients with IBS (11, 39–41). However, it has been consistently difficult to correlate its presence with any specific feature of the disorder, such as symptomatology, symptom severity, or even bowel habit (39–41). Therefore, it is not necessarily surprising that the relationship between sensitivity and hormone levels in this study is also difficult to interpret. However, although most of these correlations were rather weak with low predictive power, the fact that they were sometimes highly statistically significant and totally confined to the patient group indicate that there is probably some real underlying relationship that is worthy of further exploration.

In conclusion, our data support the need for further exploration of the role of male sex hormones in the complex issue of the pathophysiology of IBS. Furthermore, hormonal status, both male as well as female, probably needs to be taken into account much more than previously, particularly when designing new pharmacological approaches to the treatment of this condition.

Reprint requests and correspondence: L. A. Houghton, Department of Medicine, University Hospital of South Manchester, Nell Lane, West Didsbury, Manchester, M20 2LR UK.

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