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The Effects of Weight Change on the Dexamethasone Suppression Test in Depressed and Anorexic Patients

I. SCHWEITZER, K. P. MAGUIRE, J. W. G. TILLER, A. H. GEE, L. C. HARRISON and B. M. DAVIES

Prior studies on weight change and hypothalmic–pituitary–adrenal (HPA) axis functioning are reviewed. Data on 58 depressed and eight anorexic patients is presented. No significant difference in the frequency of cortisol non-suppression in the dexamethasone suppression test (DST) was found between depressed patients with a history of weight loss and those without, nor between depressed patients who lost weight during their first week in hospital and those who did not. Mean weight loss of suppressors did not significantly differ from that of non-suppressors. Of 12 patients whose DST normalised during their stay in hospital, only four gained weight. Five anorexics who were non-suppressors were $< 70\%$ of their ideal body weight (IBW), while three suppressor anorexics were $\geq 70\%$ IBW. These results indicate that mild to moderate weight change is not a significant influence on DST response in depression.

Studies of hypothalamic–pituitary–adrenal (HPA) axis functioning and its relationship to depression commenced in the 1960s (Sacher *et al*, 1970, Carroll, 1971). Early work concentrated firstly on urinary metabolites of cortisol and then on plasma cortisol levels. During the 1970s, dynamic studies of central HPA axis regulation became possible. In general, these studies have concluded that some depressed patients have altered HPA axis regulatory mechanisms similar to those found in Cushing's disease. These abnormalities include excessive cortisol secretion with increased nocturnal release, impaired responsiveness to lysine vasopressin and to hypoglycaemia and non-suppression of plasma cortisol following the administration of dexamethasone (Carroll *et al*, 1976). Due to its ease of application, the dexamethasone suppression test (DST) has been the most widely investigated test of these regulatory abnormalities and approximately 50% of depressed patients have been found to be non-suppressors of cortisol (Hirschfeld *et al*, 1983). However, the cause and mechanism of these HPA axis abnormalities remains unclear.

The relationship between weight change and alterations in HPA axis functioning has also been recognised. As weight loss is a common feature, it has been suggested that this factor alone might be responsible for non-suppression of cortisol in the DST (Edelstein *et al*, 1983). The purpose of this project was to examine this question in a systematic, prospective manner and to study several parameters of weight change in depression in relation to the DST.

Background

The interaction of weight change and HPA axis functioning may be considered under five headings.

Fasting obese subjects

Galvao-Teles *et al* (1976), found significant increases in plasma unbound cortisol in a group of 13 fasting obese subjects. These changes were most marked at 2400 h, indicating a considerable dimunition of the day–night variation of plasma unbound cortisol levels. Edelstein *et al*, (1983), studied 18 healthy, non-depressed overweight subjects before and after a protein-sparing fast. All patients received the DST and all suppressed cortisol normally before fasting. However, after 8–12 weeks of fasting, when subjects had lost an average of 14.3 kg, five (28%) of the subjects had become non-suppressors. There was no significant alteration in mood in these subjects. In both of these studies, patients were on stringent low calorie diets and lost substantial amounts of weight in a relatively brief period of time.

Fasting normal subjects

Berger *et al* (1984), studied 24 healthy volunteers who were placed on a 1000–1300 kilocalorie diet and who

lost an average of 1.5 kg/week. In nine (37.5%) of these subjects cortisol became non-suppressible to dexamethasone. Yerevanian *et al* (1984), studied 16 non-depressed volunteers and found that two (12.5%) converted from normal suppression to non-suppression after a period of strenuous dieting. Again, in both of these studies rigorous dieting was instituted resulting in sudden weight changes.

Starving subjects

Smith *et al* (1975), studied ten adult patients with protein–calorie malnutrition and found elevated levels of plasma cortisol, increased urinary excretion of cortisol, reduced metabolic clearance of cortisol, reduced plasma production rate of cortisol and non-suppression of cortisol following dexamethasone. Weight loss in all subjects was severe and several were in a state of inanition.

Anorexia nervosa patients

There are considerable data available (Weiner, 1977, Walsh, 1982) which indicate the frequent association of abnormalities of the HPA axis and anorexia nervosa. Anorexic patients have low urinary 17-OH corticosteroid levels, increased half-life of plasma cortisol, reduced metabolic clearance rate of cortisol, increased secretion rate of cortisol and elevated urinary free cortisol. Non-suppression of cortisol following dexamethasone has been found to occur in over 50% of anorexic patients (Gwirtsman & Gerner, 1981), approximating therefore the frequency in depression. These abnormalities of HPA axis functioning have been found mostly in the acute weight-loss stage of the illness when patients are less than 80% of their ideal body weight (IBW). They tend to normalise with response to treatment and gain in weight (Fichter *et al*, 1982), although this has been disputed (Gwirtsman & Gerner, 1981).

Depressed subjects with or without weight change

There have been a number of studies that have attempted to address specifically the question of the effect of weight change on the HPA axis in depressed patients. At present, results are conflicting. Carroll was the first to observe that 28 depressed subjects who had lost at least 3.2 kg in weight had significantly higher morning plasma cortisol levels than 12 subjects without such loss of weight (Carroll, 1971). Studies using the DST specifically have been of three types. One approach has been to examine the history for recorded data of recent weight change. Three studies of this type (Coppen *et al*, 1984; Zimmerman *et al*, 1984; Yerevanian *et al*, 1984), found no relationship between a history of weight loss and DST response while two studies (Kline *et al*, 1983; Targum, 1983) both with small numbers of patients contradicted this finding. A sixth study (Feinberg & Carroll, 1984) found that weight loss was a significant variable but only when considered in isolation. When severity of the illness and the age of the patient were taken into account the history of weight loss was concluded to be an insignificant variable. These retrospective studies analysed case records, mostly by using the weight change item of the Hamilton depression rating scale or the Newcastle scale. These studies are therefore open to criticism because they are dependant on the reliability and details in documentation in the history and the care with which the weight change item had been assessed.

A second approach has been to measure weight change during the first week of a period in hospital and relate this to DST response. This is based on the assumption that such weight change will reflect and correlate with recent weight changes during the depressive episode and will therefore overcome the problem of historical inaccuracy. Two such studies (Feinberg & Carroll, 1984; Holsboer *et al*, 1984) both found no relationship between weight loss and DST response, while a third found weight loss to be a significant factor (Berger *et al*, 1983).

A third approach has been to monitor changes in DST response during the period in hospital, specifically the normalisation of the response. Only one (Targum, 1983) such study has been performed to date. This study found that three patients of ten whose DST failed to normalise during 6 weeks in hospital, gave a history of weight loss at admission.

Methods

Patients admitted to the Psychiatric Unit of The Royal Melbourne Hospital (RMH) were independently assessed by two psychiatrists. Those patients meeting DSM-III criteria for major depressive disorder (MDD) were included in the study. Carroll's exclusion criteria were applied (Carroll *et al*, 1981). All patients were assessed for severity of depression within the first few days of admission, using a Hamilton observer-rating scale and a Carroll self-rating scale. In addition to a careful history of recent weight change, all patients were weighed and their height was measured at admission. Wherever possible, family members were interviewed for further information concerning weight loss. During the first week (but not before the third day following admission) all patients received a standard DST with 1 mg of dexamethasone being administered at 2300 h and blood samples for serum cortisol being taken the same and following day at 1600 h. Plasma cortisol was analysed in the Department of Biochemistry (RMH) using the routine assay (Amerlex, Amersham, UK). Normal suppression was

defined as a post-dexamethasone serum cortisol concentration of less than 167 nmol/litre, a criterion established from a previous normal control study in the unit. All patients were re-assessed at weekly intervals during their period in hospital, with Hamilton and Carroll ratings, weighings and DSTs.

In addition, a group of anorexic patients have been studied. These patients were examined by two psychiatrists and all patients met DSM-III criteria for Anorexia Nervosa. Their assessments were similar to the depressed patients with weekly weighings, Hamilton and Carroll ratings, and standard DSTs.

As appropriate, χ^2 and t-tests were performed, for statistical analysis of the data. A $P>0.05$ was used as the criterion for a non-significant (NS) result.

Results

History of recent weight loss

Of a total of 58 depressed patients studied, 29 were found to have had a recent history of significant weight loss (defined as more than 2 kg within the previous 2 months), while 29 gave no such history. Eleven of the 29 patients who had lost weight were non-suppressors of cortisol while nine of the 29 patients who had no history of weight loss were non-suppressors which represented no significant difference between the two groups (Table I). Furthermore, for the patients who had lost weight, the mean weight loss of the non-suppressors was 7 kg, while that of the suppressors was 5 kg. This difference was not significant. Also, both groups were only slightly below their mean ideal body weight (IBW), the mean for non-suppressors being 97% of their IBW and suppressors 95% of IBW.

TABLE I

Comparison of DST response, cortisol concentrations and severity of depression in the weight-loss[1] vs no weight-loss groups

	Weight-loss group (n = 29)	*No weight-loss group (n = 29)*	*Statistics*
Non-suppressors Suppressors	11 18	9 20	$\chi^2 = 0.076$ NS
1600 h Pre-dexamethasone Cortisol (nmol/litre)	380 ± 191[2]	360 ± 122	$t = -0.47$ NS
1600 h Post-dexamethasone Cortisol (nmol/litre)	195 ± 213	138 ± 150	$t = -1.18$ NS
Δ Cortisol[3]	196 ± 152	223 ± 154	$t = 0.66$ NS
Hamilton Depression Rating Score	28 ± 5	26 ± 5	$t = -1.64$ NS

1. Defined as ≧2 kg over the 2 months prior to admission
2. Mean ± SD.
3. Δ Cortisol = pre-dexamethasone cortisol − post-dexamethasone cortisol

TABLE II

DST response and weight loss during the first week in hospital (n = 49)

	Weight-loss[1] group	*No weight-loss group*
Non-suppressors	11	9
Suppressors[2]	11	18
	22	27

$\chi^2 = 0.79$
NS

1. Defined as >0.5 kg
2. Data unavailable on nine patients — early discharge or transfer or weighings missed.

The weight-loss vs the no-weight-loss groups were compared with regard to mean plasma cortisol levels obtained from the initial DST during the first week in hospital. The mean pre-dexamethasone plasma cortisol concentration, mean post-dexamethasone plasma cortisol concentration and mean change in plasma cortisol concentrations from pre- to post-dexamethasone levels were not significantly different in these two groups (see Table I). Also, there was no significant difference in the severity of depression at admission, as measured by the Hamilton depression rating scale, between the weight-loss and no-weight-loss groups (see Table I).

Weight loss as measured during the first week of stay in hospital

Of the 49 depressed patients on whom relevant data were available, 22 were found to have lost 0.5 kg or more during their first week of stay in hospital. Twenty-seven depressed patients lost no weight or gained weight during their first week. There was no significant difference in the frequency of non-suppression in the weight-loss group vs the no-weight-loss group (see Table II). Furthermore, there was no significant difference in the mean weight loss of the non-suppressor group versus the suppressor group, approximately 2 kg in each group.

Weight changes during the course of stay in hospital

Among the 58 patients studied, there were 17 non-suppressors of cortisol who completed at least 3 weeks of inpatient treatment. Of these 17 patients, 12 converted to normal suppression during their inpatient stay (mean stay 5 weeks), while five remained non-suppressors. Of the twelve patients who converted to normal suppression only four (33%) gained weight during their stay in hospital. Seven of the remaining patients did not significantly alter their weight during their hospital stays while one patient actually lost weight.

Anorexic patients

Of eight anorexia nervosa patients who were studied, five were non-suppressors at admission, while three were normal suppressors. All five non-suppressors were 70% or less of

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their IBW at admission, while the three suppressors were over 70% of their IBW. There was no apparent correlation between non-suppression and clinical assessment of depression or Hamilton depression rating score. Of the five non-suppressors, four converted to normal suppression after several weeks of inpatient treatment and did so when their weights exceeded 70% of their IBW. The one anorexic patient who remained a non-suppressor failed to respond to treatment or to gain weight.

Discussion

Studies of non-depressed groups including obese, malnourished and anorexic patients as well as normal subjects all indicate that weight loss is frequently associated with abnormalities in several tests of HPA axis functioning, including the DST. These studies suggest that either severe loss of weight or sudden substantial losses of weight will result in changes in HPA axis functioning. However, none of these groups are strictly comparable to a depressed patient population. Weight loss in depression in current clinical populations, is usually mild and gradual and only rarely severe and/or rapid. Amongst our patient group, the average weight loss reported by those patients who had lost weight prior to admission was 5.8 kg over the previous 2–3 months. There was only one patient who had lost more than 12 kg in weight and only one patient who was less than 70% of her IBW. In marked contrast in our anorexic group only those patients who were 70% or less of their IBWs were non-suppressors of the DST. Also, these patients converted to normal suppression when their weight exceeded 70% of their IBW.

The majority of the studies that have addressed the issue of weight loss in depression and the DST, conclude that weight loss is not a significant variable, whilst two studies contradict this finding. Most of these studies can be criticised from the point of view of retrospectivity and some because of low numbers and lack of definition of degree of weight loss. Although history of weight loss must by necessity be retrospective, we have attempted to overcome the problems of previous work which has largely relied on the weight change item of questionnaires. Our patients were carefully and directly questioned with regard to recent weight loss and whenever possible family members were interviewed. Also in our study, we have included a prospective and objective approach by measuring weight change weekly during the patients stay in hospital.

Our results support those prior studies which conclude that mild to moderate weight change is not a significant influence on the DST response in depression; DST response was not significantly linked to reported history of weight loss or weight loss as measured during the first week in hospital. In addition, there were 12 patients in whom the DST response normalised with treatment during their stay in hospital and in the majority of these patients (67%) there was no weight change during the corresponding period.

The cut-off point for normal suppression, a plasma cortisol of 167 nmol/litre, had been determined from a previous study of 100 normal volunteers who had undergone a standard DST—and Carroll's recommendation of 5% of a normal population as being non-suppressors was used to calculate this value. In fact, when our data was re-examined using our former cut-off point of a plasma cortisol of 138 nmol/litre, the DST status of only one patient changed, making no significant difference to our results. Also, when our data was analysed using patients' plasma cortisol concentrations rather than the suppressor vs non-suppressor category we again found history of weight loss was not a significant variable.

Although, acute and severe losses of weight may influence HPA axis functioning and consequently the DST response, this is not usually the case in depressive illness. We conclude that weight change need only be taken into account when interpreting the DST response in depressed patients, when weight loss is unusually severe or rapid.

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*I. Schweitzer, MB, BS, DPM, FRANZCP, *Senior Lecturer, Department of Psychiatry*; K. P. Maguire, BSc (Hons), MSc, PhD, *Research Scientist, Department of Psychiatry*; J. W. G. Tiller, MB, ChB, DPM, FRACP FRANZCP, *First Assistant, Department of Psychiatry*; L. C. Harrison, MD, FRACP, *Director, Endocrine Laboratory, Department of Diabetes and Endocrinology*; A. H. Gee, MB, BS, *Registrar, Department of Psychiatry; B. M. Davies, MD, DPM, FRANCZP, FRACP, FRCPsych., Professor of Psychiatry, Department of Psychiatry, University of Melbourne*

*Correspondence: *University of Melbourne, Clinical Sciences Block, Royal Melbourne Hospital, Victoria 3050, Australia*

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