Study of the Effect of Changing Glucose, Insulin, and Insulin-Like Growth Factor-I Levels on Serum Corticosteroid Binding Globulin in Lean, Obese, and Obese Subjects With Glucose Intolerance

José-Manuel Fernández-Real, Michel Pugeat, Agnés Emptoz-Bonneton, and Wifredo Ricart

We have previously described that serum corticosteroid binding globulin (CBG) concentrations are associated with insulin secretion. The present study was designed to evaluate the effects of changing insulin concentrations, both endogenous and after exogenous insulin administration, on circulating CBG levels in vivo. Serum CBG concentrations were measured during an insulin-modified frequently sampled intravenous (IV) glucose tolerance test (FSIVGT) in 14 lean and 19 obese otherwise healthy subjects with varying degrees of glucose tolerance. Acute insulin response to glucose (AIRg) correlated significantly with serum CBG concentrations at time 0 ($r = -.38$, $P = .029$), 22 minutes ($r = -.41$, $P = .01$), 50 minutes ($r = -.41$, $P = .01$), and 180 minutes ($r = -.39$, $P = .02$). Insulin sensitivity (S_I) was not associated with serum CBG concentration at time 0 ($r = -.16$, $P =$ not significant [NS]), but correlated significantly with CBG concentration at 22 minutes ($r = -.41$, $P = .02$) and 50 minutes ($r = -.35$, $P = .048$) of the FSIVGT. In lean subjects, serum CBG concentration decreased significantly after IV insulin from 37.9 ± 5.4 to 35.4 ± 3 mg/L ($P = .02$) and returned to basal levels thereafter. In contrast, obese, glucose-tolerant subjects had lower CBG levels than lean and obese glucose intolerant subjects (33.8 ± 3.0 *v* 37.9 ± 5.4 and 39.8 ± 4.4 mg/L, respectively), and their serum CBG concentrations remained unchanged during FSIVGT. Mean serum-free insulin-like growth factor-I (IGF-I) concentrations steadily declined from 1.21 ± 0.81 to 0.8 ± 0.36 μg/L during the FSIVGT, and this effect was restricted to lean subjects. Basal serum-free IGF-I did not correlate with CBG levels at time 0, but correlated inversely with the serum CBG concentrations at 22 minutes ($r = -.36$, $P = .04$). Stepwise multivariant analysis showed that AIRg ($P = .035$) and S_I ($P = .046$), but not free IGF-I levels, independently contributed to 28% of CBG variance at 22 minutes. These results suggest that insulin, but not IGF-I, constitutes an important negative regulator of CBG liver synthesis. Endogenous and exogenous insulin do not affect serum CBG concentrations in insulin-resistant obese subjects with preserved or decreased insulin secretion. Obese glucose-tolerant subjects are hypothesized to exhibit tonically inhibited serum CBG levels. In contrast, in lean subjects, the higher the insulin secretion the lower the serum CBG concentration. The mechanisms of this CBG inhibitory effect exerted by insulin and its implication on cortisol homeostasis and fat distribution in humans await further investigations.

ABNORMALITIES IN hypothalamic-pituitary-adrenal axis and cortisol production have been found to predict cardiovascular disease and type 2 diabetes.[1] Low variability and morning cortisol values, a poor lunch-induced cortisol response, and a blunted dexamethasone suppression of cortisol intercorrelated with classical risk factors for cardiovascular disease and type 2 diabetes mellitus in a recent study.[1] Corticosteroid binding globulin (CBG) is the major blood transport protein for cortisol in humans.[2,3] The regulation of CBG synthesis by liver, the main source of CBG in humans, is not well-known. Changes in diet composition may alter both insulin secretion and plasma CBG concentration.[4] The inhibitory effects of insulin and insulin-like growth factor-I (IGF-I) on CBG synthesis have been demonstrated in human hepatoblastoma-derived (HepG2) cells,[5] but little attention has been devoted to possible relationships of insulin and IGF-1 with circulating CBG levels in humans. De Moor et al[6] had reported in 1962 that some patients with uncomplicated obesity who also show a low morning plasma cortisol level have marked decrease in CBG binding capacity.

Circulating cytokines, such as interleukin-6 (IL-6), may affect both insulin sensitivity (S_I)[7] and CBG concentrations.[8-10] IL-6 also decreased CBG synthesis by HepG2 cells.[11,12] Serum CBG concentration seems to be related to glucose homeostasis. In a recent study, we found that CBG levels were associated with fasting glucose (positively) and with the insulin response to intravenous (IV) glucose (negatively).[13] Both insulin and IGF-1 concur to maintain normal glucose levels,[14] and IGF-1, especially in the fasting state, exerts a tonic effect on glucose homeostasis.[15] In lean subjects, circulating free IGF-I concentrations change inversely with fasting blood glucose and, interestingly, IGF-I levels decrease during a frequently sampled intravenous glucose tolerance test (FSIVGT).[16] In the present study, we investigated the effects of acute changes in plasma glucose, insulin, and IGF-1 levels during an insulin-modified FSIVGT on serum CBG concentrations in obese and nonobese, healthy men and women.

SUBJECTS AND METHODS

Study Population

Three groups of subjects were prospectively studied: 14 lean (L), 9 obese (Ob), and 10 obese subjects with glucose intolerance (Ob-Intol). Inclusion criteria were: (1) body mass index (BMI) (weight in kilograms divided by the square of height in meters) greater than 30 and less than 40 kg/m^2 for obese and less than 27 (men) or less than 25 kg/m^2 (women) for lean subjects, (2) absence of any systemic disease, and (3) absence of any infections in the previous month. None of the subjects were taking any medication (including glucocorticoids or estrogens) or had any evidence of metabolic disease other than obesity.

From the Unitat de Diabetologia, Endocrinologia i Nutricio, University Hospital of Girona, "Dr Josep Trueta", Girona, Spain; and the Hospices Civils de Lyon, Laboratoire de la Clinique Endocrinologique, Hôpital de l'Antiquaille, and INSERM U329, Lyon, Cedex, France.

Submitted January 2, 2001; accepted February 8, 2001.

Address reprint requests to José-Manuel Fernández-Real, MD, PhD, Unitat de Diabetologia, Endocrinologia i Nutricio, University Hospital of Girona, "Dr Josep Trueta", Carretera de França s/n, 17007 Girona, Spain.

0026-0495/01/5010-0030$35.00/0
doi:10.1053/meta.2001.25647

Table 1. Anthropometrical and Biochemical Variables in the Study Subjects

Variable	Lean	Obese	Obese-Intolerant	ANOVA *P*
No.	14	9	10	—
Men/women	8/6	5/4	5/5	NS
Age (yr)	36 ± 5.3	37.2 ± 6.5	39.8 ± 3.8	NS
BMI (kg/m^2)	22.7 ± 2.9*	32.2 ± 2.3	32.6 ± 2.4	<.00001
WHR	0.94 ± 0.06	1.00 ± 0.05	1.01 ± 0.06	.036
Fasting glucose (mmol/L)	5 ± 0.59	4.98 ± 0.47	6.2 ± 1.05†	.0005
Fasting insulin (mU/L)	7.8 ± 3.14‡	9.6 ± 3.1	15.1 ± 8.4	.0058
AIRg (mU/L)	367 ± 195§	755 ± 414	250 ± 217§	.0034
Insulin sensitivity (min^{-1}/mU/L)	3.8 ± 1.6*	2.26 ± 0.55	0.99 ± 0.98	.0002
CBG (mg/L)	37.9 ± 5.4	33.8 ± 3	39.8 ± 4.4§	.037
Free IGF-I (ng/L)	1.21 ± 0.81	0.96 ± 0.45	0.99 ± 0.58	NS

Abbreviations: AIRg, acute insulin response to intravenous glucose; CBG, corticosteroid binding globulin; NS, not significant.
*Significantly different from the obese group and obese-intolerant group ($P < .05$).
†Significantly different from the obese and lean groups ($P < .05$).
‡Significantly different from the obese-intolerant group ($P < .05$).
§Significantly different from the obese group ($P < .05$).

The subjects reported that their body weight had been stable for at least 3 months before the study; they were normotensive and normolipemic (the latter data is not shown) with normal liver and thyroid function that were checked by normal biochemical workup. The women in this study had regular menstrual cycles; they were investigated on days 3 to 8 of 2 consecutive menstrual cycles. The protocol was approved by the Hospital Ethics Committee, and informed consent was obtained from each subject.

Procedures

The subjects' waists were measured with a soft tape midway between the lowest rib and the iliac crest. The hip circumference was measured at the widest part of the gluteal region. Blood pressure was measured in the supine position on the right arm after a 10-minute rest; a standard sphygmomanometer of appropriate cuff size was used, and the first and fifth phases were recorded. The subjects were required to consume a weight-maintaining diet containing at least 300 g of carbohydrate per day and refrained from exertion for 3 days before the study. The subjects also abstained from caffeine and alcohol for 72 hours before the tests. An oral glucose tolerance test (OGTT) was performed according to the recommendations of the National Diabetes Data Group.[17] After a 12-hour overnight fast, glucose was ingested in a dose of 75 g, and blood samples were collected through a venous catheter from an antecubital vein at 0, 30, 60, 90, and 120 minutes for measurement of serum glucose.

S_I was analyzed using the insulin-modified FSIVGT with minimal model analysis as described elsewhere.[13] In brief, the experimental protocol started between 8:00 and 8:30 AM after an overnight fast. A butterfly needle was inserted into an antecubital vein, and patency was maintained with a slow saline drip. Basal blood samples were drawn at -30, -10, and -5 minutes, after which glucose (300 mg/kg body weight) was injected over 1 minute starting at time 0. Regular insulin (0.03 U/kg) was injected at 20 minutes. Additional samples were obtained from a contralateral antecubital vein until 180 minutes.

The serum glucose level during the FSIVGT was measured in duplicate by the glucose oxidase method with a glucose analyzer 2 (Beckman, Brea, CA). The coefficient of variation was 1.9%. The serum insulin level during the FSIVGT was measured in duplicate by monoclonal immunoradiometric assay (IRMA; Medgenix Diagnostics, Fleunes, Belgium). The lowest limit of detection was 4.0 mU/L. The intraassay coefficient of variation was 5.2% at a concentration of 10 mU/L and 3.4% at 130 mU/L. The interassay coefficients of variation were 6.9% and 4.5% at 14 and 89 mU/L, respectively.

CBG and Free IGF-I Measurements

The protein concentration of CBG was measured by using a radioimmunoassay as previously described.[7] We included in each of the 6 CBG immunoassays of this study 3 samples with different concentrations of CBG for calculating the interassay variability: 37 ± 2, 48 ± 3, and 116 ± 11 (± SD) giving respective variability of 5.4%, 6.2%, and 9.4%.

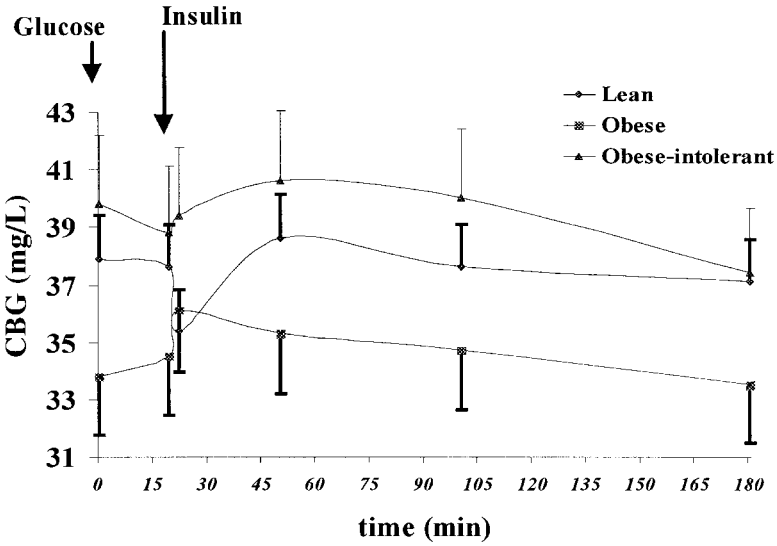
Free IGF-I was determined at times 0, 19, 22, 50, 100, and 180 minutes. These times were selected according to the study by Nyomba et al.[16] We used the 2-site immunoradiometric assay (IRMA) kit (Diagnostic Systems Laboratories; Webster, TX)) for measuring free (or freely dissociated) IGF fraction. This method is highly sensitive and has been used as a direct assay to measure the dissociable fraction of IGF-I, which is considered the free IGF-I fraction. The detection limit was 0.03 μg/L, with an intra-assay variation less than 10% for concentrations below 2 μg/L.

Data analysis. Data from the FSIVGT were submitted to computer programs that calculate the characteristic metabolic parameters by fitting glucose and insulin to the minimal model that describes the times course of glucose and insulin concentrations. The estimation of model parameters was performed according to the Minimal Model (MINMOD) computer program.[18] Insulin secretion from the FSIVGT was calculated as the incremental insulin response from 0 to 10 minutes after IV glucose (acute insulin response to glucose [AIRg]).

Statistical analysis. Descriptive results of continuous variables are expressed as mean ± SD. Before statistical analysis, normal distribution and homogeneity of the variances were tested. Parameters that did not fulfill these tests (CBG at the different points, AIRg, free IGF-I levels at the different points, and S_I) were log-transformed. We used χ^2 test for comparisons of proportions. Comparison of variables across the 3 groups of subjects was performed by 1-way analysis of variance (ANOVA) using Fisher's test for multiple comparisons. Levels of statistical significance were set at $P < .05$.

RESULTS

Table 1 shows anthropometric and biochemical characteristics of the subjects. The 3 groups of nonobese or obese glucose-tolerant or obese, glucose-intolerant subjects were comparable in sex and age, and the 2 obese groups were similar in BMI and waist-to-hip ratio (WHR) (Table 1). Obese-intolerant subjects showed higher fasting and postload glucose levels and higher



CBG (mg/l)	Basal	19 min	22 min	50 min	100 min	180 min
Lean Subjects (n=14)	37.9 ± 5.4	37.6 ± 4.4	35.4 ± 3[a]	38.6 ± 4.8	37.6 ± 5.1	37.1 ± 4.5
Obese Subjects (n=9)	33.8 ± 3[a]	34.5 ± 2.5[b]	36.1 ± 2.8	35.3 ± 3.6[b]	34.7 ± 3.3	33.5 ± 3.8[b]
Obese-Intolerant Subjects (n=10)	39.8 ± 4.4	38.8 ± 2.8	39.4 ± 5.1	40.6 ± 3.7	40 ± 4.4	37.4 ± 3

Fig 1. Time course of serum CBG levels during insulin-modified FSIVGT. [a]*P* < .05 *v* obese-intolerant group; [b]*P* < .01 *v* obese-intolerant group.

fasting insulin levels than the other groups of subjects; they also displayed impaired insulin secretion after IV glucose and a nonsignificant different S_I index as compared with obese glucose-tolerant individuals. In addition, obese-intolerant subjects had significantly higher serum CBG levels than nonobese and obese, glucose-tolerant subjects (39.8 ± 4.4 *v* 37.9 ± 5.4 and 33.8 ± 3.0 mg/L, respectively; $P < .05$).

FSIVGT Studies

To determine the dose-response effects of insulin on free IGF-I and CBG levels, changes in their respective serum concentrations were measured during insulin-modified FSIVGT. Serum insulin increased from 7.8 ± 3.1 mU/L to a peak of 49 ± 26 mU/L in lean subjects, from 9.6 ± 3.1 mU/L to 121 ± 75 mU/L in obese subjects, and from 15.1 ± 8.4 mU/L to 60.4 ± 42 mU/L in obese-intolerant subjects after 4 minutes of glucose injection and declined gradually thereafter. Injection of insulin at 20 minutes resulted in a maximal elevation in serum insulin to 310 ± 123 mU/L in lean subjects, 398 ± 79 mU/L in obese subjects, and 431 ± 86 mU/L in obese-intolerant subjects. Insulin concentration returned to basal levels by 60 minutes in the control group and by 120 minutes in the obese groups.

The time courses of free IGF-I and CBG levels during the FSIVGT are shown in Figs 1 and 2. Serum-free IGF-1 levels remained virtually unchanged in the obese groups. In contrast, in lean subjects, a mean 34% steady suppression of serum-free IGF-I was observed.

Serum CBG levels significantly declined at 22 minutes in lean subjects ($P = .022$) and returned to approximately their basal levels at 50 minutes ($P = .008$). In contrast, there were no significant changes in serum CBG in both obese groups. By the end of the FSIVGT, both free IGF-I and CBG returned to their basal levels.

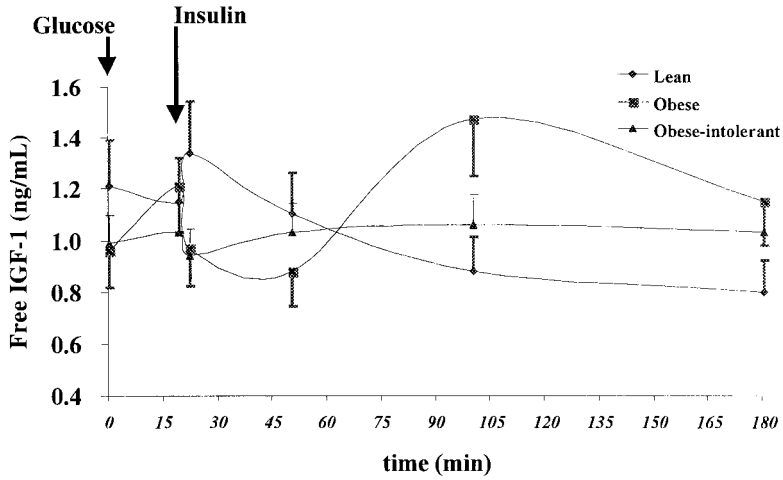
AIRg was associated with serum CBG concentration, AIRg being significantly correlated with CBG in basal conditions ($r = -.38$, $P = .029$) and at 22 ($r = -.41$, $P = .01$), 50 ($r = -.41$, $P = .01$), and 180 ($r = -.39$, $P = .02$) minutes after glucose stimulation of endogenous insulin secretion. S_I did not predict basal serum CBG ($r = -.16$, $P =$ not significant [NS]), but the former was associated with serum CBG concentrations at 22 ($r = -.41$, $P = .02$) and 50 ($r = -.35$, $P = .048$) minutes of FSIVGT.

Fasting insulin levels correlated significantly with serum-free IGF-I levels ($r = -.35$,$P = .04$). Free IGF-I levels steadily declined during the FSIVGT in lean subjects, a finding that was not observed in obese subjects. Basal serum-free IGF-I significantly correlated with serum CBG at 22 minutes ($r = -.36$, $P = .04$), but not at 50 minutes ($r = -.32$, $P = .07$) during FSIVGT.

Stepwise multivariant analysis showed that AIRg ($P = .035$) and S_I ($P = .046$), but not free IGF-I levels, could predict CBG levels at 22 minutes and independently contributed to 28% of the variance in CBG levels.

DISCUSSION

According to our results, serum CBG concentration in humans decreases significantly after IV infusion of glucose, and this decrease differs according to glucose tolerance and body fatness. Obese subjects with normal glucose tolerance show lower basal CBG levels, which are negatively associated with insulin secretion. These results suggest that the higher insulin concentration of obese subjects might tonically inhibit CBG



Free IGF-I (ng/l)	Basal	19 min	22 min	50 min	100 min	180 min
Lean Subjects (n=14)	1.21 ± 0.81	1.15 ± 0.77	1.34 ± 1.03	1.1 ± 0.54	0.88 ± 0.48 *	0.8 ± 0.36 *
Obese Subjects (n=9)	0.96 ± 0.45	1.21 ± 0.62	0.97 ± 0.87	0.88 ± 0.74	1.47 ± 0.88	1.15 ± 0.67
Obese-Intolerant Subjects (n=10)	0.99 ± 0.58	1.03 ± 0.71	0.94 ± 0.65	1.03 ± 0.62	1.06 ± 0.59	1.03 ± 0.42

Fig 2. Time course of serum-free IGF-I levels during insulin-modified FSIVGT. *$P < .05$ *v* basal levels.

levels, but fails to further decrease CBG after acute insulin secretion. In contrast, obese glucose-intolerant subjects show higher CBG levels[13] and impaired insulin secretion that is not sufficient to decrease CBG levels after glucose challenge.

Physiologic increments in plasma insulin concentrations have selective effects on the synthesis of hepatic proteins in normal humans.[19] Insulin is able to promote albumin distribution to peripheral tissues by increasing the protein transcapillary escape rate.[20] We describe here that the insulin response after a glucose challenge was associated with acute changes in CBG levels. Portal insulin concentrations are approximately 3-fold higher than peripheral insulin concentrations,[21] possibly explaining a greater impact of endogenous insulin secretion. This result is in line with the insulin dose-dependent inhibition of CBG secretion by HepG2 cells.[5] It suggests that insulin is involved in the chronic adjustments of serum CBG concentration and might regulate acute changes in serum CBG levels in physiologic circumstances of normal insulin secretion. This effect of endogenous insulin could explain the 20% decrease in plasma CBG of normal man after a high carbohydrate diet.[4]

S_I in our patients was not associated with basal CBG levels, a finding that is in agreement with our previous report.[13] However, both AIRg and S_I predicted CBG at 22 minutes. Serum CBG concentration significantly decreased at 22 minutes. This CBG change could be related to endogenous insulin secretion, the cumulative effects of both endogenous and exogenous insulin effects, or a change in vascular tone after insulin administration.[22] The independent association between S_I and CBG at 22 minutes might explain why serum CBG levels were not modified in insulin-resistant, obese subjects. Interestingly, a moderate, but significant, increase of CBG has been described in diabetic patients,[23] and in addition, 1 epidemiologic study has shown that high plasma CBG was associated with increased incidence of type 2 diabetes.[24] If we establish a parallelism with another binding protein, lower serum CBG level could be relevant in cortisol homeostasis because a decrease in IGF-BP rapidly affects free IGF-I levels.

Free IGF-I levels and S_I were also found to be associated with acute changes in serum CBG on univariant analysis. In in vitro studies IGF-I decreased CBG mRNA expression and CBG protein secretion by HepG2 cells dose-dependently, and, in fact, IGF-I was more potent than insulin in performing such effects.[5] We found that when controlling for AIRg and S_I, IGF-I was no longer associated with changing CBG levels. This discrepancy might be in relationship with the very high level of IGF-I receptor mRNAs in HepG2 cells in contrast to the virtual absence of IGF-I receptors in normal human hepatocytes (Crave et al, personnal communication, May 2000). All of this evidence suggest that IGF-I has no physiologic effect on liver CBG synthesis and that insulin is a confounding factor of the association between IGF-I and CBG.

A significant decrease in free IGF-I levels after glucose challenge has been described by Nyomba et al[16] in healthy subjects. Our data confirmed that observation, but it was restricted to nonobese subjects.

In summary, obese subjects show tonically inhibited serum CBG levels, which are not further modified after acute glucose and insulin changes. In nonobese subjects, insulin could constitute a regulator of serum CBG level when insulin secretion is preserved. The consequences of acute or chronic CBG decreases on cortisol homeostasis and their impact on fat distribution should be further investigated.

REFERENCES

1. Rosmond R, Bjorntorp P: The hypothalamic-pituitary-adrenal axis activity as a predictor of cardiovascular disease, type 2 diabetes and stroke. J Intern Med 247:188-197, 2000
2. Hammond GL: Molecular properties of corticosteroid-binding globulin and the sex-steroid binding proteins. Endocr Rev 11:65-79, 1990
3. Rosner W: The functions of corticosteroid binding globulin and the sex-hormone binding globulin: Recent advances. Endocr Rev 11: 80-91, 1990
4. Anderson KE, Rosner W, Khan MS, et al: Diet-hormone interactions: Protein/carbohydrate ratio alters reciprocally the plasma levels of testosterone and cortisol and their respective binding globulins in man. Life Sci 40:1761-1768, 1987
5. Crave JC, Lejeune H, Brébant C, et al: Differential effects of insulin and insulin-like growth factor I on the production of plasma steroid-binding globulins by human hepatoblastoma-derived (Hep G2) cells. J Clin Endocrinol Metab 80:1283-1289, 1995
6. De Moor P, Heirwegh K, Heremans JF, et al: Protein binding of corticoids studied by gel filtration. J Clin Invest 41:816-827, 1962
7. Fernández-Real JM, Broch M, Vendrell J, et al: Interleukin 6 and insulin sensitivity. Diabetes 49:517-520, 2000
8. Pugeat M, Bonneton A, Perrot D, et al: Decreased immunoreactivity and binding activity of corticosteroid-binding globulin in serum in septic shock. Clin Chem 35:1675-1679, 1989
9. Bernier J, Jobin N, Emptoz-Bonneton A, et al: Decreased corticosteroid-binding globulin in burn patients: Relationship with interleukin-6 and fat and nutritional support. Crit Care Med 26:452-460, 1998
10. Tsigos C, Kyrou I, Chrousos GP, et al: Prolonged suppression of corticosteroid-binding globulin by recombinant human interleukin-6 in man. J Clin Endocrinol Metab 83:3379, 1998 (letter)
11. Bartalena L, Hammond GL, Farsetti A, et al: Interleukin-6 inhibits cortisosteroid-binding globulin synthesis by human hepatoblastoma-derived (HepG2) cells. Endocrinology 133:291-296, 1993
12. Emptoz-Bonneton A, Crave JC, Lejeune H, et al: Corticosteroid-binding globulin synthesis regulation by cytokines and glucocorticoids in human hepatoblastoma-derived (HepG2) cells. J Clin Endocrinol Metab 82:3758-3762, 1997
13. Fernández-Real JM, Grasa M, Casamitjana R, et al: Plasma total and glycosylated corticosteroid-binding globulin levels are associated with insulin secretion. J Clin Endocrinol Metab 84:3192-3196, 1999
14. Clemmons DR, Underwood LE: Nutritional regulation of IGF-I and IGF binding proteins. Annu Rev Nutr 11:393-412, 1991
15. Giacca A, Fisher SJ, Shi ZQ, et al: Insulin-like growth factor-I and insulin have no differential effects on glucose production and utilization under conditions of hyperglycemia. Endocrinology 134: 2251-2258, 1994
16. Nyomba BL, Berard L, Murphy LJ: Free insulin-like growth factor-I (IGF-I) in healthy subjects: Relationship with IGF-binding proteins and insulin sensitivity. J Clin Endocrinol Metab 82:2177-2181, 1997
17. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 28:1039-1057, 1979
18. Bergman RN, Prager R, Volund A, et al: Equivalence of the insulin sensitivity index in man derived by the minimal model method and euglycaemic glucose clamp. J Clin Invest 79:790-800, 1987
19. De Feo P, Volpi E, Lucidi P, et al: Physiological increments in plasma insulin concentrations have selective and different effects on synthesis of hepatic proteins in normal humans. Diabetes 42:995-1002, 1993
20. Hilsted J, Christensen NJ: Dual effects of insulin on plasma volume and transcapillary albumin transport. Diabetologia 35:99-103, 1992
21. Blackard WG, Nelson NC: Portal and peripheral vein immunoreactive insulin concentrations before and after glucose infusion. Diabetes 19:302-306, 1970
22. Yki-Jarvinen H, Utriainen T: Insulin-induced vasodilatation: Physiology or pharmacology? Diabetologia 41:369-379, 1998
23. De Moor P, Heyns W: Cortisol binding capacity of plasma transcortin in diabetics patients. J Clin Endocrinol Metab 27:706-708, 1967
24. Linstedt G, Lundberg PA, Lapidus L, et al: Low sex hormone-binding globulin concentration as independent risk factor for developement of NIDDM. 12-yr follow up of population study of women in Gothenburg, Sweden. Diabetes 40:123-128, 1991