Insulin Secretion, Glucose Production, and Insulin Sensitivity in Underweight and Normal-Weight Volunteers, and in Underweight and Normal-Weight Cancer Patients: A Clinical Research Center Study

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Severe malnutrition (<65% ideal body weight [IBW]) is associated with reduced insulin secretion, decreased receptor affinity, and glucose intolerance. To characterize the abnormality of mild malnutrition in terms of insulin action, both the insulin sensitivity index and insulin secretion were measured in 15 underweight and 15 normal-weight volunteers. Ten patients had localized squamous cell carcinomas of the head and neck, and 20 were normal controls. After a 10-hour overnight fast, all volunteers were studied using Bergman's modified intravenous (IV) glucose tolerance test (IVGTT). Body weight and diagnosis were compared using a 2 × 2 ANOVA. The acute insulin response to IV glucose was reduced in normal-weight and underweight cancer patients by approximately 40% to 50% ($P < .05$). Both groups of cancer patients had a significantly reduced rate of glucose disposal (1.25 ± 0.29 and 1.27 ± 0.23 %/min) compared with the healthy volunteers (1.82 ± 0.21 and 1.81 ± 0.24 %/min, respectively, $P < .05$). Glucose production (GP) was significantly increased in the underweight cancer patients versus the weight-matched volunteers (13.9 ± 1.3 *v* 10.8 ± 0.5 μmol/kg/min, $P < .05$). Normal-weight and underweight cancer patients had a 32% to 44% reduction in insulin sensitivity ($P < .05$). In contrast to the effects of cancer, underweight controls had twice the insulin sensitivity compared with normal-weight controls ($P < .01$). Since insulin secretion decreased in underweight controls, the increased insulin sensitivity may have been due to an increased insulin action and to factors associated with leanness.

GLUCOSE INTOLERANCE is commonly observed in severe malnutrition (ideal body weight [IBW] 65% of normal), due to decreased insulin secretion.[1] In diabetes, severe malnutrition decreases insulin secretion, glucose disposal, and hepatic insulin receptor affinity.[2] The alterations of insulin sensitivity with mild weight loss are not well documented in either cancer patients or normal volunteers. Animal studies have demonstrated that early malnutrition is associated with a transient increase in insulin sensitivity.[3] Euglycemic-hyperinsulinemic clamp studies in non–tumor-bearing animals have demonstrated that early malnutrition increases the ability of insulin to inhibit endogenous glucose production (GP) and to stimulate glucose disposal.[4]

The insulin response to an oral glucose load is normal in cancer patients compared with weight-matched volunteers.[5,6] No studies have documented the insulin response to an intravenous (IV) glucose tolerance test (IVGTT) in weight-matched patients with a single tumor type.[5] The paucity of data on insulin sensitivity and insulin secretion in underweight adults and cancer patients prompted this study.

In an attempt to clarify the importance of body weight and cancer to glucose tolerance, we studied 15 underweight (<100% IBW) and 15 normal-weight subjects. Ten had head and neck cancer, and 20 were normal volunteers. We selected the modified IVGTT to evaluate the secretory capacity of the β cell to both glucose and an insulin secretagogue (tolbutamide), and to determine the glucose disposal rate. The modified IVGTT was selected because it can identify early abnormalities in glucose tolerance that may provide insight into the mechanism(s) responsible for changes in insulin sensitivity. Our hypothesis was that tumor necrosis factor-alpha (TNF-α) concentrations would be elevated in underweight cancer patients and that these concentrations would be inversely correlated with insulin sensitivity.

SUBJECTS AND METHODS

Fifteen normal-weight (≥100% IBW) volunteers (with and without cancer) were compared with 15 underweight (<100% IBW) volunteers (with and without cancer). No one was physically active (exercise > once per week: jogging, etc.), and all of the cancer patients were ambulatory and not restricted to bed. No one had a family history of diabetes. Fasting plasma glucose concentrations were measured in all volunteers before obtaining informed consent. Any volunteer with a fasting blood glucose greater than 6.7 mmol/L, overt diabetes mellitus, or clinical evidence of cirrhotic liver disease, renal disease, or anemia (hematocrit < 30) was excluded.

All volunteers consumed a 200-g carbohydrate diet 3 days before study. The mean 24-hour dietary food intakes were similar for cancer patients (2,110 ± 330 cal/d, mean ± SEM) and normal-weight volunteers (2,420 ± 520). Cancer patients and normal volunteers were admitted to the Clinical Research Center at Harbor-UCLA Medical Center under Internal Review Board approval. IBW was determined using the Metropolitan Life Tables based on age, gender, and height. The Clinical Research Center dietitian performed standardized anthropometry, measuring triceps skinfolds and mid-arm circumference of the left arm with established methods. Muscle mass was estimated with the formula used by Forbes and Bruining,[7] using height and mid-arm muscle area.

After an overnight fast, in vivo insulin sensitivity and insulin secretory patterns were measured using the modified IVGTT.[8] This model uses a computed mathematical analysis to relate the change in plasma insulin to plasma glucose clearance after a 1-minute bolus of IV glucose (300 mg/kg body weight), followed 20 minutes later by an IV bolus of tolbutamide (500 mg). Plasma glucose and insulin concentra-

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tions were measured at −15, −10, −5, −1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 minutes though a double-stopcock system. C-peptide, glucagon, growth hormone (GH), cortisol, insulin-like growth factor-I (IGF-I), TNF-α, and thyroid hormone levels were measured at time zero. Insulin, C-peptide,[9] growth hormone,[10] cortisol,[11] glucagon,[12] TNF-α,[13] and thyroid hormone levels were measured using established methods. IGF-I level was measured as acid ethanol–extracted IGF-I as previously described.[14] Serum protein levels, liver function, and cholesterol concentrations were measured in the hospital clinical chemistry laboratory. Glucose level was measured with an ABA-100 analyzer (Abbott, South Pasadena, CA) by a glucose oxidase method.

The next morning, a primed, continuous (25 μCi, 0.3 μCi/min) infusion of 6-^{3}H-glucose (100% pure; New England Nuclear, Boston, MA) was administered over a 4-hour period. Blood was obtained for glucose specific activity at 180, 200, 220, and 240 minutes as previously described.[15] Five normal volunteers and two cancer patients elected not to complete the radioactive infusion study on day 3.

Data analysis was performed using both the BMDP biostatistical package and the Bergman modified minimal model program.[8] Fractional glucose disposal was determined as a first-order rate constant from 8 to 19 minutes. The total insulin area under the time curve was determined by summation of the area determined by the formula for a trapezoid. The acute plasma insulin response was determined by measuring the mean insulin response at 2, 3, 4, 5, 6, 8, and 10 minutes after IV glucose. The insulin response after IV tolbutamide was also determined as the mean response at 22, 23, 24, 25, 27, and 30 minutes. In both cases, the baseline insulin concentration (time zero and time 20, respectively) was subtracted from the mean response. A 2 × 2 ANOVA was performed with (1) underweight versus normal-weight and (2) cancer versus noncancer comparisons. Simple linear regression analysis and multiple-step regression analysis were performed using the method of least squares. Significance was defined as P less than or equal to .05.

RESULTS

Patient Characteristics

Ten patients with localized head and neck cancer and 21 normal volunteers were screened. One normal patient was found to have an elevated fasting glucose, and was therefore eliminated from the data analysis. Six cancer patients were stage IV, one stage III, two stage II, and one stage I at the time of study. There was no evidence of metastatic disease. Two patients were studied at the time of tumor recurrence 14 and 6.5 months after the initial diagnosis. One had surgery and radiation therapy, and one had radiation therapy alone. Both returned to medical care with a new tumor recurrence, and were studied within 7 days of diagnosis. Patients were studied after mean of 12 ± 7 days from diagnosis of the primary tumor (n = 8) or recurrence (n = 2). None of the patients had received chemotherapy before the study. All volunteers were without known diabetes or recent infections. Table 1 describes patient characteristics. Normal-weight cancer volunteers were older than normal-weight noncancer volunteers. Underweight groups (cancer and noncancer) had similar anthropometric measurements (Table 1). Muscle mass and fat area were also similar.

Fasting insulin was higher and IGF-I and triiodothyronine (T_3) lower in cancer patients (Table 2). Fasting thyroxine, GH cortisol, and TNF-α concentrations were normal. Being underweight was associated with a mild reduction in fasting insulin and C-peptide concentrations (Table 2). Serum protein, uric acid, cholesterol, and glucagon concentrations and liver-function tests were not different among the four groups (data not shown).

Table 1. Patient Characteristics and Anthropometric Data (mean ± SEM)

Parameter	Normal-Weight		Underweight	
	Normals (n = 11)	Cancer Patients (n = 4)	Normals (n = 9)	Cancer Patients (n = 6)
Age (yr)	48 ± 2	60 ± 2	48 ± 3	52 ± 3*
Weight (kg)	83 ± 4	83 ± 9	64 ± 3	50 ± 4†
BMI (kg/m^2)	26.5 ± 0.6	26.2 ± 2.5	19.9 ± 0.6	17.5 ± 0.8†
IBW (%)	112 ± 2	114 ± 9	86 ± 3	75 ± 3†
MAC (cm)	52 ± 4	51 ± 4	38 ± 3	28 ± 4†
TSF (mm)	18 ± 2	17 ± 5	10 ± 1	8 ± 2†
Mid-arm fat (cm^2)	33 ± 4	32 ± 11	15 ± 2	10 ± 2†
Muscle mass (kg)	32 ± 2	31 ± 2	24 ± 3	18 ± 3†

Abbreviations: BMI, body mass index; IBW, ideal body weight; MAC, mid-arm circumference; TSF, triceps skinfold thickness.

*$P \leq .05$ by ANOVA, cancer groups *v* normal groups.

†$P \leq .01$ by ANOVA, normal-weight (cancer patients and normals) *v* underweight (cancer patients and normals).

Insulin Secretion

The acute insulin response was significantly reduced by 40% to 50% in cancer patients (Fig 1A and B). Cancer had no effect on the post-tolbutamide amount of insulin secretion (+2% for normal-weight and −23% for underweight respectively, $P > .05$). Total insulin secretion over the 180 minutes was not reduced in the cancer groups (−10% for normal-weight and −30% for underweight, $P > .05$). Underweight individuals, independent from the effects of cancer, had a 40% (range, 37% to 43%) reduction in total insulin secretion ($P < .05$), which may have been secondary to a smaller glucose load (300 mg/kg body weight). This is supported by the observed lower instantaneous glucose (Go) at time zero (Table 3). Total insulin secretion was directly correlated with BMI (Fig 2).

Insulin Sensitivity

Cancer patients had a 32% to 44% reduction in insulin sensitivity ($P < .05$) compared with weight-similar healthy

Table 2. Fasting Hormonal Profile (mean ± SEM)

Variable	Normal-Weight		Underweight	
	Normals	Cancer Patients	Normals	Cancer Patients
Insulin (pmol/L)	66 ± 9	82 ± 4	35 ± 5	67 ± 10*†
C-peptide (μg/L)	0.31 ± 0.09	0.33 ± 0.03	0.15 ± 0.03	0.27 ± 0.03†
Cortisol (μg/dL)	9.9 ± 1.9	8.9 ± 0.8	12.3 ± 2.1	13.1 ± 3.8
GH (μg/L)	0.8 ± 0.3	0.5 ± 0.1	2.1 ± 1.1	2.9 ± 1.4‡
IGF-I (μg/L)	316 ± 26	250 ± 29	295 ± 25	217 ± 30*
T_3 (nmol/L)	1.72 ± 0.17	1.18 ± 0.35	1.55 ± 0.17	1.13 ± 0.18*
Thyroxine (nmol/L)	80 ± 6	86 ± 27	71 ± 9	73 ± 9
TNF-α (pg/mL)	12.8 ± 0.6	11.2 ± 0.2	14.1 ± 1.8	13.5 ± 0.7

*$P \leq .05$ for cancer effect by ANOVA, cancer groups *v* normal groups.

†$P \leq .05$ for body weight effect by ANOVA, normal-weight (cancer patients and normals) *v* underweight (cancer patients and normals).

‡$P = .08$ by ANOVA, normal-weight *v* underweight.

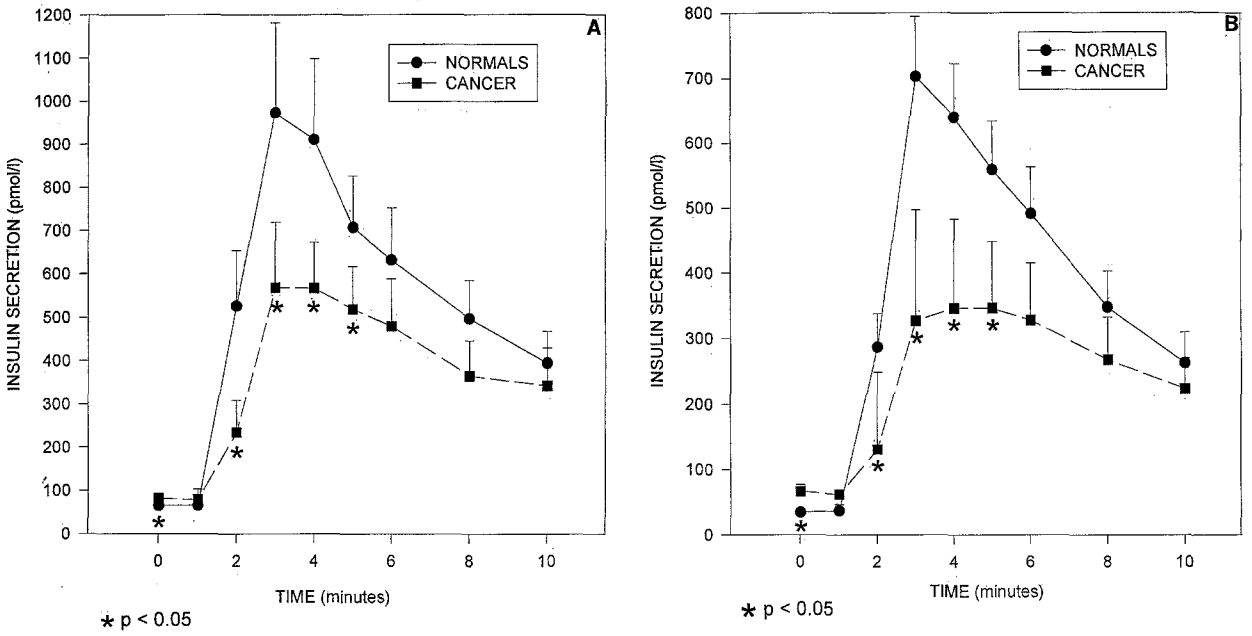

Fig 1. Acute insulin response to IV glucose for (A) normal-weight and (B) underweight volunteers. Cancer patients had a significantly reduced acute insulin response as the area under the time curve and at 2, 3, 4, and 5 minutes ($P < .05$). Note different Y-axis scale.

controls (Table 3). However, insulin sensitivity increased greater than twofold (110%) in underweight healthy volunteers and increased 65% in underweight cancer volunteers (Table 3) compared with the respective normal-weight groups.

Glucose Metabolism

The volume of glucose distribution was slightly but not significantly increased in the cancer volunteers (Table 3). Glucose disposal was significantly reduced by 30% in the cancer groups compared with the normal controls. Glucose disposal was similar in underweight and normal-weight controls (1.82 and 1.81 %/min) and cancer patients (1.25 and 1.27 %/min). Consistent with a decrease in glucose disposal, cancer patients had a significant reduction in insulin sensitivity (Table 3).

Multiple-step regression analysis ($r^2 = .72$, $P < .001$) of the current data demonstrated that glucose disposal was correlated directly with the T_3 concentration ($r = .48$, $P < .05$), insulin sensitivity index ($r = .44$, $P < .05$), and acute insulin response ($r = .42$, $P < .05$) and inversely correlated with the volume of glucose distribution ($r = -.67$, $P < .05$). The lower T_3 concentration and first-phase insulin response suggests that these two factors may have contributed to the reduced glucose disposal observed in cancer patients.

Table 3. Glucose Parameters and Insulin Sensitivity in Volunteers and in Head and Neck Cancer Patients Following IV Glucose and Tolbutamide Administration (mean ± SEM)

	Normal-Weight		Underweight	
Parameter	Normals	Cancer Patients	Normals	Cancer Patients
Insulin secretion, time 0 to 180 (pmol/min)	438 ± 80	338 ± 91	274 ± 52	194 ± 34†
Instantaneous glucose at time 0 (mmol/L)	15.8 ± 0.3	16.1 ± 2.0	13.8 ± 0.4	12.5 ± 0.8‡
Glucose distribution (L)	13.9 ± 0.4	15.0 ± 1.7	13.3 ± 0.8	13.5 ± 1.3
Glucose disappearance (%/min)	1.82 ± 0.21	1.25 ± 0.29	1.81 ± 0.24	1.27 ± 0.23*
Insulin sensitivity ($min^{-1} \cdot 10^{-4}$)/μU/mL	2.5 ± 0.4	1.7 ± 0.5	5.2 ± 0.7	2.8 ± 0.5*‡

*$P \leq .05$ for cancer effect by ANOVA, cancer groups *v* normal groups.

†$P \leq .05$ and ‡$P < .01$ for body weight effect by ANOVA, normal-weight (cancer patients and normals) *v* underweight (cancer patients and normals).

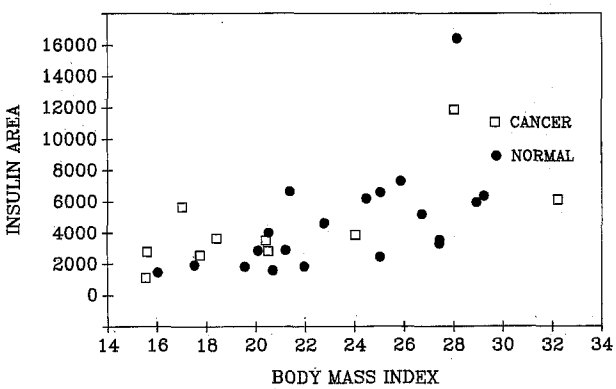

Fig 2. Correlation between BMI (kg/m^2) and total insulin secretion (pmol/180 min) determined as area under the curve (time 0 to 180 minutes). (□) Cancer patients; (●) normal volunteers ($r = .582$, $P < .05$). As BMI decreases, insulin secretion increases in both cancer patients and normal volunteers.

Independent from the cancer, insulin sensitivity was significantly increased in underweight cancer (2.8 *v* 1.7 $min^{-1} \cdot 10^{-4}$/(μU/mL), $P < .05$) and underweight normal volunteers (5.2 *v* 2.5, $P < .05$; Table 3). This observation suggests that a decrease in adiposity (leanness) can increase insulin sensitivity.

Insulin Sensitivity and Anthropometry

Body weight, as a percent of IBW, was inversely correlated with insulin sensitivity in healthy volunteers ($r = -.655$, $y = 13.18 - 0.094x$, $n = 20$, $P < .005$) and cancer patients ($r = -.610$, $y = 5.28 - 0.032x$, $n = 10$, $P = .06$). Adiposity, as estimated by BMI, was also inversely correlated with insulin sensitivity in both normal volunteers ($r = -.64$, $y = 12.26 - 0.36$, $n = 20$, $P < .05$) and cancer patients ($r = -.65$, $y = 5.35 - 0.14x$, $n = 10$, $P < .05$; Figs 3A and B). Upper-arm fat area was also inversely correlated with insulin sensitivity for normal volunteers ($r = -.52$, $P < .05$) and cancer patients ($r = -.63$, $P \leq .05$). These data would suggest that adiposity as estimated by either BMI or upper-arm fat area is inversely correlated with insulin sensitivity.

Hepatic GP

Hepatic GP was significantly elevated in the underweight cancer patients compared with noncancer volunteers (Table 4). Fasting glucose concentrations were also increased in both cancer groups. GP was directly correlated with serum cortisol in the underweight cancer group ($r = .63$, $P < .05$) and in the normal-weight volunteers ($r = .46$, $P < .05$).

Table 4. Fasting Hepatic GP (mean ± SEM)

	Normal-Weight		Underweight	
	Normals	Cancer Patients	Normals	Cancer Patients
Glucose production (μmol/kg/min)	10.1 ± 0.4	10.1 ± 0.6	10.8 ± 0.5	13.9 ± 1.3*†
Fasting glucose concentration (mmol/L)	5.8 ± 0.1	6.4 ± 0.4	5.7 ± 0.1	6.1 ± 0.3*

*$P < .05$ for cancer effect by ANOVA, cancer groups *v* normal groups.

†$P < .01$ for body weight effect by ANOVA, normal-weight (cancer patients and normals) *v* underweight (cancer patients and normals).

DISCUSSION

Insulin Sensitivity in Underweight Individuals

This study has demonstrated that being underweight (with and without cancer) increases insulin sensitivity. Similar to what has been demonstrated here, underweight animals have an increase in insulin sensitivity[3] until they are severely malnourished[1,2] (<65% of usual weight[1,2]). Our most underweight individuals had a body weight at 67% of IBW (cancer patient) and 68% of IBW (normal volunteer). Their insulin sensitivity was increased at 4.73 and 4.57 $min^{-1} \cdot 10^{-4}$/U/L), respectively. Our data confirm that insulin sensitivity was significantly increased in the underweight individuals. The site of the increased insulin sensitivity (muscle or liver) is not known.

Insulin sensitivity in the muscle increases by 70% in patients with anorexia nervosa when measured by a euglycemic-hyperinsulinemic clamp method.[16] However, anorexia nervosa may not typify simple malnutrition. Glucose utilization in underweight individuals (body weight, 49.3 ± 5.0 kg) increases above normal after refeeding.[17] However, the rate of glucose disposal was not increased in the underweight volunteers (cancer patients or normals), which suggests that insulin sensitivity was due to an increased insulin effectiveness.

Insulin Secretion in Malnutrition

Total insulin secretion was reduced by 40% in the underweight (normals and cancer patients) individuals. This similar reduction in total insulin secretion in the underweight groups does not account for the significant reduction in insulin sensitivity seen in cancer patients and normal volunteers (Table 3). However, the lower first-phase insulin secretion in the cancer groups (Figs 1A and B) may have been responsible for the reduced insulin sensitivity seen in cancer. The explanation for the increased insulin sensitivity in both underweight groups is not known.

Besides the effects of malnutrition, insulin secretion also decreases with advancing age. Although the cancer patients were older, there was no correlation between age and insulin

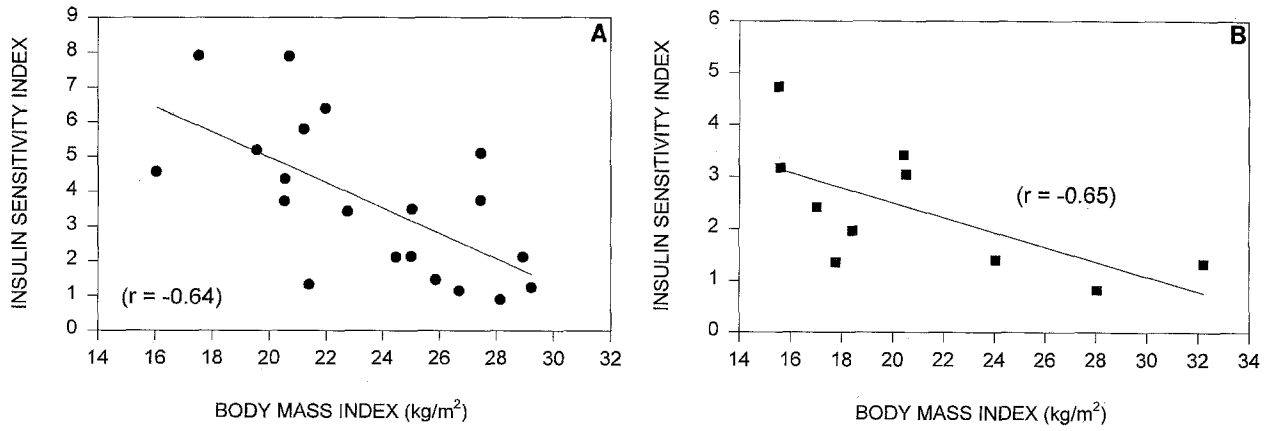

Fig 3. BMI is inversely correlated with the insulin sensitivity index. (A) Significant correlation for (●) normal volunteers ($r = -.64$, $P < .05$). (B) Significant correlation for (■) cancer patients ($r = -.65$, $P < .05$).

secretion or action. Weight loss in NIDDM and obese patients reduces proinsulin and insulin secretion, increases insulin clearance, and improves insulin sensitivity.[18] A reduced total insulin secretion may be secondary to an improved insulin sensitivity. A recent study suggests that an abnormal insulin action may be more responsible for glucose intolerance than a blunting of insulin secretion.[19] In cancer patients, a 40% reduction in the first-phase insulin secretion may be the cause of the decreased insulin sensitivity observed in cancer, but another mechanism, such as elevated hepatic GP, may be responsible.

Insulin Resistance in Cancer

The reduced first-phase insulin secretion, decreased glucose disposal, and increased glucose production seen in the cancer volunteers is similar to that seen in type II diabetes.[1,19,20] Cancer volunteers, like diabetics, have a reduced hepatic sensitivity to insulin.[20,21] Low-dose insulin administration, under euglycemic clamp conditions, fails to rapidly suppress endogenous GP.[20,21] Fasting GP is not always elevated in normal-weight cancer patients,[5,20] but is commonly elevated in normal-weight patients with sarcoma[21] or lung cancer.[5] Approximately 70% of underweight cancer patients have an elevated GP.[5] GP increases as malnutrition progresses in cancer patients.[5,22] It is unlikely that a 30% increase in GP seen in the underweight cancer patients would reduce insulin sensitivity. If this were true, one would expect GP to be elevated by a similar degree in the normal-weight cancer patients (Table 4).

Glucose disposal was reduced by 30% in both the normal-weight and underweight cancer volunteers (Table 3). Dogs with lymphoma also have a 30% reduction in glucose disposal.[24] Patients with pancreatic,[23] colon,[25] head and neck,[20] or gastrointestinal[26] cancer or lymphoma[27] have a reduced glucose utilization by the euglycemic-hyperinsulinemic glucose clamp technique. Unlike the discordant effects of weight loss on GP, both normal-weight and underweight cancer patients have a reduced glucose utilization.[26] As early as 48 hours after a tumor resection, glucose utilization returns toward normal.[26] This has been confirmed by others to occur 14 days after colon cancer surgery.[25] The rapid nature of this improvement would suggest that one mechanism responsible may be tumor-mediated.

Another explanation for the reduced glucose disposal may be an increase in the volume of glucose distribution. A 14% increase in our patients was similar to a 15% increase observed by Reichard et al[28] in a small group of head and neck cancer patients. A 40% to 47% increase in the volume of glucose distribution has been observed in patients with colon and gastrointestinal carcinomas.[29,30] The increased glucose pool size was associated with an increase in glucose carbon recycling.[29,30] However, a larger volume of distribution would only contribute to insulin insensitivity if the glucose distribution was to non–insulin-sensitive tissues (tumor, etc.).

Hormonal Factors Associated With Glucose Metabolism

TNF-α was a likely candidate to explain the reduced insulin sensitivity in cancer patients, but fasting plasma TNF-α was not correlated with the observed abnormalities in insulin action. Unlike what has been reported previously,[31] TNF-α was not elevated or correlated with glucose disposal. Serum cortisol, while not significantly elevated in the cancer groups, was significantly correlated with GP in the normal-weight volunteers and underweight cancer patients. Serum cortisol has recently been demonstrated to be directly correlated with gluconeogenesis in normals and cancer patients.[32] The decreased glucose utilization and elevated GP may be due to an insulin resistance associated with an increased cortisol secretion.

Earlier studies suggested that GH may increase GP in cancer patients,[22] since it is commonly elevated in malnutrition. However, GH administration failed to simulate GP,[33] and GP was not correlated with an elevated GH secretion.[34]

IGF-I concentration was significantly reduced in both groups of cancer patients. IGF-I administration fails to increase nonoxidative glucose disposal,[35] so it is unlikely that the observed reduction in IGF-I was responsible for the decrease in glucose disposal.

Reductions in thyroid hormone have been implicated as a factor contributing to a reduced glucose utilization.[20,36] Patients with head and neck cancer have a reduced glucose utilization that is correlated ($r = .66$) with T_3 concentration.[20] T_3 has also been directly correlated with both oxidative and nonoxidative glucose utilization in normal volunteers.[36] Multiple-step regression analysis ($r^2 = .72$, $P < .001$) of the current data demonstrated that glucose disposal was directly correlated with the T_3 concentration, insulin sensitivity index, and acute insulin response and inversely correlated with the volume of glucose distribution. The lower T_3 concentration and the correlation with glucose disposal suggest that T_3 may have contributed to the reduced insulin sensitivity. A prospective study testing this hypothesis will be required to confirm this observation.

Insulin Sensitivity and Adiposity

Normal volunteers have an inverse relationship of insulin sensitivity with a BMI that ranges from 52.2 to 19.5.[37] Our data demonstrate that this relationship also continues to a BMI as low as 15.5 (Fig 3). While insulin sensitivity increased, the rate of glucose disposal was unchanged. This would suggest that the increased insulin sensitivity was associated with an increased insulin effectiveness at the site of the liver for normal volunteers. Animal research in undernutrition has demonstrated that noncancer littermates who are 70% of normal weight have an increased insulin sensitivity at the liver and skeletal muscle as measured by a euglycemic-hyperinsulinemic clamp.[4] Underweight individuals in our study did not have an increased glucose disposal, but did have increased insulin sensitivity.

In summary, underweight volunteers have a significant increase in insulin sensitivity that is most likely due to their reduced adiposity and increased insulin action. On the other hand, normal-weight and underweight cancer patients have a blunted first-phase insulin response, reduced glucose disposal, and reduced insulin sensitivity. The reduced T_3 concentration in cancer patients was directly correlated with glucose disposal and may have contributed to the reduced insulin sensitivity. Underweight cancer patients also had a significant elevation in fasting GP, which suggests that insulin resistance occurs at both the muscle and the liver. The increased insulin sensitivity in normal volunteers may have been due to the greater first-phase insulin response to IV glucose. The reasons for a blunting of the

first-phase insulin response and a reduced glucose disposal in cancer volunteers are not known.

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