Aging exaggerates the blood glucose response to total parenteral nutrition

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Objective: To determine the effect of age on the blood glucose and insulin responses to a clinical model of glucose loading (i.e., total parenteral nutrition [TPN] with hypertonic glucose), in patients with a variety of conditions.

Design: A prospective cohort study.

Setting: An adult university hospital.

Patients: Seventy-one consecutive, clinically stable patients receiving central TPN, excluding those with metabolic disease or receiving relevant medications.

Intervention: None.

Main Outcome Measures: Serum levels of glucose, insulin, C-peptide and cortisol determined in peripheral venous blood obtained immediately before initiating TPN and again 48 to 96 hours later; acute physiology score (APS) and habitual level of physical activity (HAL).

Results: Serum levels of glucose, insulin and C-peptide increased following initiation of TPN (all $p < 0.001$). The serum glucose level during TPN administration increased as a function of both patient age and severity of illness (APS) ($r^2 = 0.37$, all $p < 0.01$), whereas the serum insulin level was inversely related to age and increased as a function of serum glucose, glucose rate of infusion and HAL ($r^2 = 0.57$, all $p < 0.05$). The serum C-peptide:insulin molar ratio did not vary with age.

Conclusions: Aging and severity of illness interact to exaggerate the increases in blood glucose that accompany TPN with hypertonic glucose. Serum insulin responses to TPN decline with aging, likely reflecting reduced insulin secretion. Diminished insulin responses may contribute to hyperglycemia and represent a diminished anabolic signal in such patients. The acutely ill elderly patient is predisposed to hyperglycemia and should be monitored carefully even when pre-TPN blood glucose values are normal.

Objectif : Déterminer l'effet de l'âge sur les réactions de la glycémie et de l'insuline à un modèle clinique de charge de glucose (c.-à-d. nutrition parentérale totale [NPT] avec glucose hypertonique) chez les patients atteints de toutes sortes d'affections.

Conception : Étude prospective de cohortes.

Contexte : Hôpital universitaire pour adultes.

Patients : Soixante et onze patients consécutifs, cliniquement stables, qui ont reçu une NPT centrale. On a exclu ceux qui avaient des problèmes du métabolisme ou qui prenaient des médications pertinentes.

Intervention : Aucune.

Principales mesures des résultats : Taux sériques de glucose, d'insuline, de peptide C et de cortisone déterminés dans le sang veineux périphérique prélevé immédiatement avant le début d'une NPT et, de nouveau, de 48 à 96 heures plus tard; score physiologique de gravité (SPG) et niveau habituel d'activité physique.

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RÉSULTATS : Les taux sériques de glucose, d'insuline et de peptide C ont augmenté après le début de la NPT (tous $p < 0,001$). Le taux de glucose sérique au cours de l'administration de la NPT a augmenté en fonction à la fois de l'âge du patient et de la gravité de la maladie (SPG) ($r^2 = 0,37$, tous $p < 0,01$), tandis que le taux d'insuline sérique présentait une relation inverse avec l'âge et a augmenté en fonction du taux de glucose sérique, du taux d'infusion du glucose et du niveau habituel d'activité physique ($r^2 = 0,57$, tous $p < 0,05$). Le ratio molaire peptide C:insuline sérique n'a pas varié en fonction de l'âge.

CONCLUSIONS : Le vieillissement et la gravité de la maladie interagissent pour aggraver les hausses de la glycémie qui accompagnent une NPT avec glucose hypertonique. Les réactions de l'insuline sérique à la NPT diminuent avec le vieillissement, ce qui reflète probablement une baisse de la sécrétion d'insuline. Des réactions réduites de l'insuline peuvent contribuer à une hyperglycémie et représentent une baisse du signal anabolique chez de tels patients. Le patient âgé gravement malade est prédisposé à l'hyperglycémie et il faut le suivre attentivement, même lorsque les valeurs de la glycémie avant la NPT sont normales.

Normal aging is accompanied by predictable changes in glucose homeostasis, which include minor increases in fasting blood glucose levels, impaired tolerance of glucose loads and diminished tissue sensitivity to insulin.[1,2] Changes in carbohydrate metabolism are also central among the metabolic responses to acute surgical illness; they include hyperglycemia, glucose intolerance and resistance of normally insulin-sensitive tissues to its effects.[3] We have observed that increases in fasting blood glucose levels after trauma are exaggerated in older patients and that such patients are markedly intolerant of short-term (2-hour) glucose loads.[4,5] To determine whether comparable age effects occur in a clinical model of glucose loading (i.e., total parenteral nutrition [TPN] with hypertonic glucose administered over a period of days), we evaluated the serum glucose, insulin and C-peptide responses to TPN in patients hospitalized with a variety of illnesses.

Patients and methods

Consecutive, clinically stable patients for whom central venous TPN with hypertonic (20%) glucose was planned as the sole nutrient source were eligible for study. Those with a history of diabetes mellitus, pregnant, or receiving corticosteroids or ß-adrenergic blocking agents were excluded. Severity of illness was evaluated in terms of acute physiology score (APS) and ward versus intensive care unit (ICU) location.[6] The reference period for the APS was the 24 hours immediately before initial blood sampling. Habitual level of physical activity (HAL) before hospitalization was assessed according to a standardized descriptive scale.[7]

Peripheral venous blood was obtained immediately before the start of TPN and again 48 to 96 hours after for determination of the serum glucose level, by glucose oxidase methodology (Glucose Analyzer 2; Beckman Instruments, Palo Alto, Calif.) and serum insulin, C-peptide and cortisol levels by radioimmunoassay (Euro/DPC, Witney, UK). TPN was provided as 4.25% or 7% amino acids (Aminosyn II 7%; Abbott Laboratories, Saint-Laurent, Que.) in 20% dextrose and lipid emulsion 10% or 20% (Liposyn II 20%; Abbott Laboratories). The rates of infusion of glucose, lipid and protein at the time of the second blood sampling were recorded, together with specific diagnoses, information on the administration of insulin and other clinical data.

Data are given as means (and standard deviations) and were analysed by unpaired and paired *t*-tests, the χ^2 test with Yates' correction and linear regression (SystatFPU 5.2.1; Systat Inc., Evanston, Ill.). The protocol was approved by the Research Ethics Committee of the Ottawa Civic Hospital, and written consent was obtained from each patient or next of kin.

Findings

Seven of 78 patients studied received exogenous insulin after the start of TPN. They were similar in age to those who did not receive insulin but had higher blood glucose concentrations before initiation of TPN ($p < 0.001$). All patients who received exogenous insulin were in an ICU ($p < 0.05$). These seven patients were excluded from further analysis. The remaining 71 patients (42 men, 29 women) ranged in age from 18 to 83 years (Fig. 1). Diagnoses were heterogeneous (Table I), and the APS ranged from 0 to 30. Thirty-two patients were in an ICU at the time of study. They had a higher APS ($p < 0.001$) and serum cortisol level ($p < 0.05$) than the 39 ward patients, but their serum glucose and insulin levels were not different. The mean age of patients in the ICU was also greater (62 [16] v. 51 [17] years, $p < 0.01$), but there was considerable overlap in

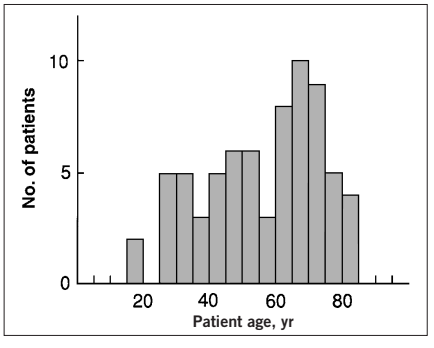

FIG. 1. Age distribution of patients (5-year intervals).

ages, and age ranges were similar (25 to 83 v. 18 to 82 years respectively). The relationship between age and severity of illness (APS), although significant ($p < 0.05$), was very limited ($r^2 = 0.08$). Patient age and HAL were weakly related ($r^2 = 0.17$, $p < 0.05$), the HAL tending to decline with age.

Serum glucose levels before the initiation of TPN did not vary with patient age, APS, HAL, weight, body mass index or the rate of glucose administered in pre-TPN intravenous solutions. Serum insulin levels were somewhat related to HAL ($r^2 = 0.20$, $p < 0.05$), tending to increase with an increased level of physical activity. Serum C-peptide levels and C-peptide:insulin molar ratios increased with the severity of illness (APS) ($r^2 = 0.21$ and 0.25, respectively, both $p < 0.001$), but neither was a function of age. Serum cortisol levels increased with increasing age and with diminished HAL ($r^2 = 0.38$, all $p < 0.01$).

The interval from the initiation of TPN to the second blood sampling did not vary with patient age. The rate of TPN administration at that time was equivalent to 1540 (383) nonprotein calories per 24 hours (25 [10] kcal/kg every 24 hours, range 700 to 2440 kcal/kg every 24 hours), comprising glucose 920 (250) kcal/24 h and lipid 620 (245) kcal/24 h, together with protein 57 (16) g/24 h (1.0 [0.4] g/kg every 24 hours). Protein, total nonprotein calories, and glucose and lipid calories administered, expressed either in absolute terms or as a function of body weight, did not vary with patient age. Patients in the ICU were receiving an average of 20% less glucose at the time of the second blood sampling than ward patients ($p < 0.01$) and a greater proportion of nonprotein calories as lipid ($p < 0.05$).

Serum glucose, insulin and C-peptide levels increased after TPN was begun, whereas serum cortisol levels did not (Table II). None was influenced by the duration of TPN administration before blood sampling. Serum glucose levels during TPN administration increased as a function of age ($p < 0.05$) and APS ($p < 0.01$), but were most strongly related to the age–APS interaction and pre-TPN glucose levels ($r^2 = 0.37$, all $p < 0.01$) (Fig. 2). Serum glucose levels were not influenced by the rate of glucose infusion. Although not related to age on univariate analysis, serum insulin levels during TPN administration declined with increasing patient age and increased as a function of the serum glucose level, rate of infusion of glucose and HAL ($r^2 = 0.57$, all $p < 0.05$) on multivariate analysis. Serum insulin levels were not related to the rate of amino acid infusion or serum cortisol level. Serum C-peptide levels increased with APS ($r^2 = 0.27$, $p < 0.001$), but neither C-peptide levels

Table I

Clinical Settings in Which 71 Patients Received Total Parenteral Nutrition (TPN)

Clinical setting	No. of patients
Ileus after abdominal sepsis or surgery	14
Multiple organ dysfunction	15
Fistula (intestinal, pancreatic, lymph)	13
Acute pancreatitis	8
Multiple trauma including abdomen	5
Bone marrow transplant	4
Other (enteritis, colitis, short-bowel syndrome)	12
Total	71

Table II

Measurements of Serum Levels Before and During TPN (Means [and Standard Deviations])

Measurement	Before TPN	During TPN
Glucose, mmol/L	5.9 (1.4)	7.5 (2.8)*
Insulin, pmol/L	80 (79)	261 (217)*
C-peptide, nmol/L	1310 (1270)	2820 (2490)*
Cortisol, nmol/L	558 (276)	518 (187)

*$p < 0.001$ v. before TPN

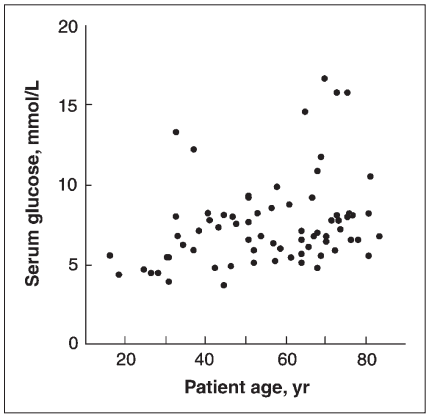

FIG. 2. Serum glucose concentrations after initiation of total parenteral nutrition, as function of age in patients with heterogeneous diagnoses and varying severities of illness.

nor C-peptide:insulin molar ratios varied with patient age.

Discussion

Carbohydrate metabolism after trauma and during sepsis has been well characterized in previously healthy young and middle-aged patients: hyperglycemia is usual despite normal or elevated serum insulin levels, endogenous glucose production is accelerated, tissues that are normally sensitive to the effects of insulin become relatively insensitive and tolerance of glucose loads is diminished.[8–11] The magnitude of these changes tends to reflect the severity of the stress, at least after injury,[4,12] and we observed that serum glucose levels during TPN increased with the severity of illness in patients with a wide variety of diagnoses.

Generally predictable changes in glucose metabolism accompany normal aging as well. Age-related changes include minor increases in fasting blood glucose levels and impaired tolerance of glucose loads, and they interact with those that follow injury.[1,2] We have observed in previous work that aging was associated with increasing fasting serum glucose levels during both the initial "ebb" and the later, hypermetabolic "flow" phases of the injury response.[4] We have also demonstrated a substantial reduction in the tolerance of an acute (2-hour) glucose load in older trauma patients, associated with markedly reduced insulin responses.[5] The present observations extend those of earlier studies in that responses to glucose loading in a clinical form (i.e., TPN) were evaluated over longer periods (at least 48 hours) in patients hospitalized with a variety of acute conditions. Serum glucose was found to increase as a function of both patient age and severity of illness. This relationship was noted despite the considerable range of diagnoses, the limited screening of patients for diabetes and other chronic conditions, the exclusion of patients who received exogenous insulin (i.e., those who were most hyperglycemic) and the heterogeneous effects of aging itself.[13] Moreover, no direct account was taken of the many factors that potentially influence glucose tolerance such as bed rest, renal insufficiency and administration of morphine, although they are presumably reflected in part in the APS and location (ward v. ICU).[14,15] It is also likely that patients in whom glucose intolerance and hyperglycemia were anticipated were administered smaller glucose loads; for example, patients in the ICU were receiving somewhat less glucose at the time of the second blood sampling than were ward patients. Despite these sources of variability, blood glucose responses to TPN were significantly influenced by patient age and severity of illness, and particularly by the interaction of these two factors.

Glucose is the most important stimulus to insulin secretion, and prompt and sustained increases in peripheral serum insulin levels during parenteral nutrition with hypertonic glucose have long been recognized.[16,17] Insulin responses to hyperglycemia are preserved in healthy, unstressed older people, but they are altered by stresses such as injury.[2,5] The insulin responses of older trauma patients to acute glucose loading have been shown to be markedly decreased compared with those of young patients.[5] The inverse relationship between age and serum insulin during TPN administration in this study is consistent with such observations, and age-related increases in blood glucose levels may have been, in part, a result of lower serum insulin concentrations. The ages of patients who received exogenous insulin were similar to those who did not; that older patients were not overrepresented among the former may reflect the small number of such patients, that all seven were in an ICU, where surveillance may be more frequent and insulin administered at a lower threshold, or that severity of illness is a more powerful determinant of hyperglycemia than age. Whether aging influences the insulin resistance that follows injury and other acute stresses also remains to be determined. The elderly patient is also predisposed to hyperglycemia by an increased threshold for the renal clearance of glucose,[18] but urine glucose levels were not measured in this study.

The age-related decline in the serum insulin level that we observed may have resulted from decreased pancreatic secretion of insulin or increased clearance from the circulation. C-peptide is a byproduct of insulin biosynthesis, co-secreted from the pancreatic beta cell on an equimolar basis with insulin, and a marker of insulin secretion.[19] The absence of an age effect on C-peptide:insulin molar ratio during TPN administration is consistent with diminished insulin secretion (rather than accelerated clearance) as the explanation for lower serum insulin levels in older patients, although it may simply reflect a lack of statistical power. A number of factors other than serum glucose influence insulin secretion. Insulin secretion is generally stimulated by amino acids and in settings of hypercortisolemia, but we did not observe statistical relationships between serum insulin and the rate of amino acid infusion or serum cortisol.[19] We did observe a modest, direct relationship between habitual physical activity and serum insulin levels, both before and during TPN infusion. This contrasts with observations in healthy subjects, in whom higher levels of habitual

physical activity are associated with increased tissue sensitivity to insulin and decreased insulin responses to glucose.[20–22] However, bed rest for periods of several days or more is accompanied by significant increases in insulin levels and diminished glucose tolerance.[14,23] The relationships among insulin secretion and clearance, tissue sensitivity to insulin and physical activity are likely to be considerably perturbed by the combined effects of age and acute illness. For example, the change to very limited physical activity that accompanies illness and hospitalization may be associated with more marked increases in serum insulin in previously active individuals.

In summary, blood glucose levels during TPN increased as a function of age in a heterogeneous group of hospitalized patients, whereas serum insulin responses decreased. Careful surveillance for hyperglycemia after initiating TPN is essential in the elderly even when previous blood glucose values have been within the normal range and especially in the most aged and most acutely ill patients. Hyperglycemia should be controlled with exogenous insulin, and consideration should be given to the use of lipid to provide an increased proportion of nonprotein calories in such patients. The diminished anabolic signal represented by impaired insulin responses in the elderly may also be disadvantageous, since the muscle mass and strength of the elderly patient are predictably reduced even before acute illness or injury.

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