

Entry Level Clinical Nutrition Part XVI

Insulin:
More than just a glycemic
hormone

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***Quality of life issues are the
major concerns more than
ever now.***

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Dr. Jeff Moss

Summer of Work Exposes Medical Students to System's Ills • NYTimes.com Page 1 of 3

The New York Times

September 9, 2009

Summer of Work Exposes Medical Students to System's Ills

By Jacob R. Gershowitz

SEATTLE — This summer, medical students from the University of Washington took a long look under the hood of the health care system they are about to inherit, and many returned to campus last week with their eyes wide open and their fists clenched.

Summer of work exposes medical students to system's ills, *The New York Times*, September 9, 2009

The students learned not only to deliver babies and suture wounds, but also to order unnecessary tests as protection against lawsuits, to hector specialists into seeing Medicaid patients, to march patients with prescriptions on Wal-Mart's 34 list. And they saw firsthand what Mr. Olguard called "a tidal wave of chronic disease" — diabetes, hypertension, obesity, depression — that left many questioning how much any one physician could really accomplish.

"I often wondered what we were actually doing to help people," Mr. Olguard said.

"...a tidal wave of chronic illness..."

For 21 years, the University of Washington School of Medicine has dispatched its rising second-year students across the Northwest to provide primary care in rural or underserved areas. The monthlong program is elective, but a record number of students took part this year — 117 from a class of 246.

The school has a cooperative agreement to train medical students from Alaska, Idaho, Montana and Wyoming, none of which has a medical college of its own. The summer program is one of several vehicles, along with loan forgiveness enticements, designed to lure students back to their home states to practice in areas with a shortage of primary care doctors.

This year, the students set out as negotiations were intensifying in Washington over wholesale changes to the health care system they will soon be joining. Whether there will be improvements to the system remains to be seen, but few students returned thinking there was time to lose.

http://www.nytimes.com/2009/09/09/health/policy/09medschool.html?_r=1&sh=4&sm=4&st=4 9/9/2009

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**Nestlé Nutrition Workshop Series
Clinical & Performance Program, Vol. 8**

**Nutrition and
Critical Care**

**Luc Cynober
Frederick A. Moore**

**Baracos VE. Overview on
metabolic adaptation to
stress, pp. 1-13.**

"An understanding of the nature of stress is fundamental to the rational design of nutrient mixtures to feed patients whose homeostasis has been altered by one or more stressors."

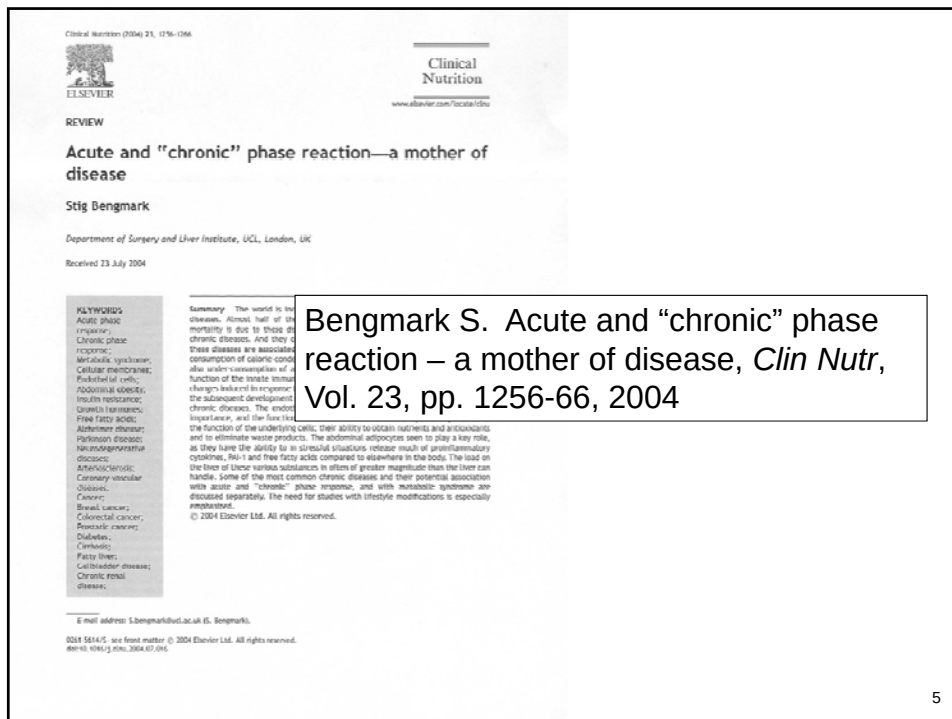
"All stresses may be presumed to be associated with characteristic modifications in the metabolism of lipids, carbohydrates, amino acids, and micronutrients."

KARGER **Nestlé NUTRITION**

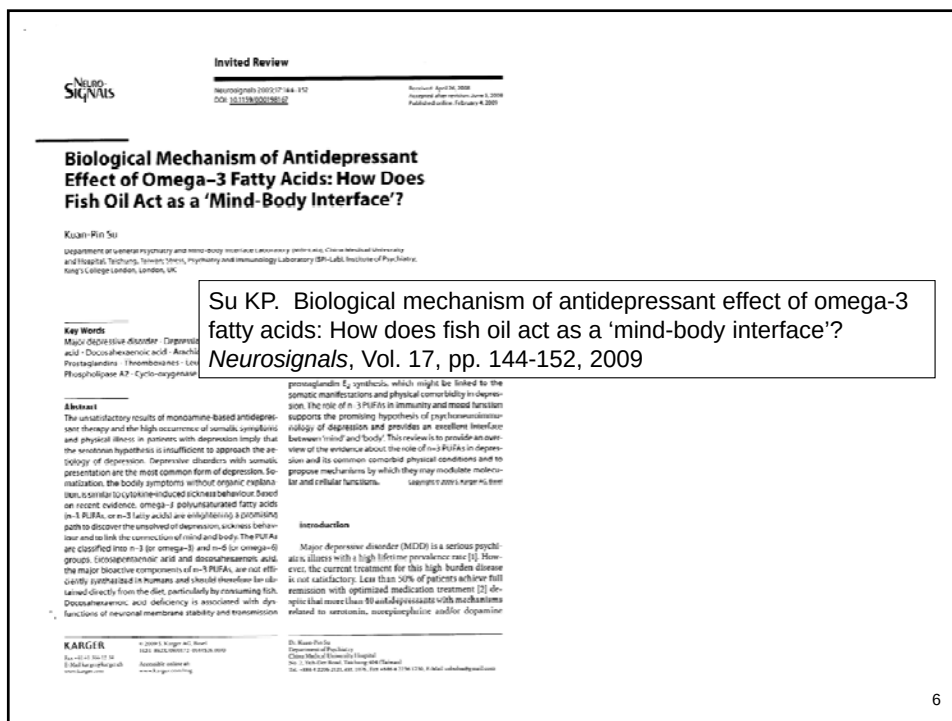
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Table 1. Overlapping of symptoms of acute sickness behaviour associated with IFN- α therapy and the somatic symptoms in MDD

Symptoms	Prevalence in IFN- α therapy ^a , %	Prevalence in MDD ^b , %
Fatigue/asthenia	39–90	73
Headache	27–67	33 ^e
Gastrointestinal symptoms	50 ^{c, 1}	34–47 ^f
Psychomotor slowing	40 ^c	59–65 ^f
Insomnia	20–39 ^d	63
Irritability	35 ^d	50
Arthralgia	9–36	31 ^e
Musculoskeletal pain	26–32	62–80 ^{g, 2}
Abdominal pain	15–20	21 ^c
Anorexia	13–19	40
Anxiety	13–18 ^d	57
Poor concentration	14 ^d	51

^a [46], unless otherwise specified; ^b [99], unless otherwise specified; ^c [100]; ^d [101]; ^e [102]; ^f [103]; ^g [104].

¹ Nausea, vomiting, bowel problems.

² Result from depressed inpatient population.

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Key metabolic imbalances seen with the acute phase response

- Metabolic acidosis
- Loss of lean body mass (sarcopenia)
- Insulin resistance
- Inflamm-aging (Increased innate immunity and decreased adaptive immunity)
- Suboptimal caloric intake and carbohydrate:protein ratio (Refeeding syndrome)
- Gastrointestinal dysfunction/gut atrophy
- Deficiencies of key micronutrients such as zinc, selenium, and vitamin D

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Underlying hypotheses of Entry Level Clinical Nutrition:

- Chief complaints in chronically ill patients are not diseases but responses that have gone on too long (Allostatic load).
- The metabolic imbalances that combine to form this response have been well defined by critical care nutritionists.

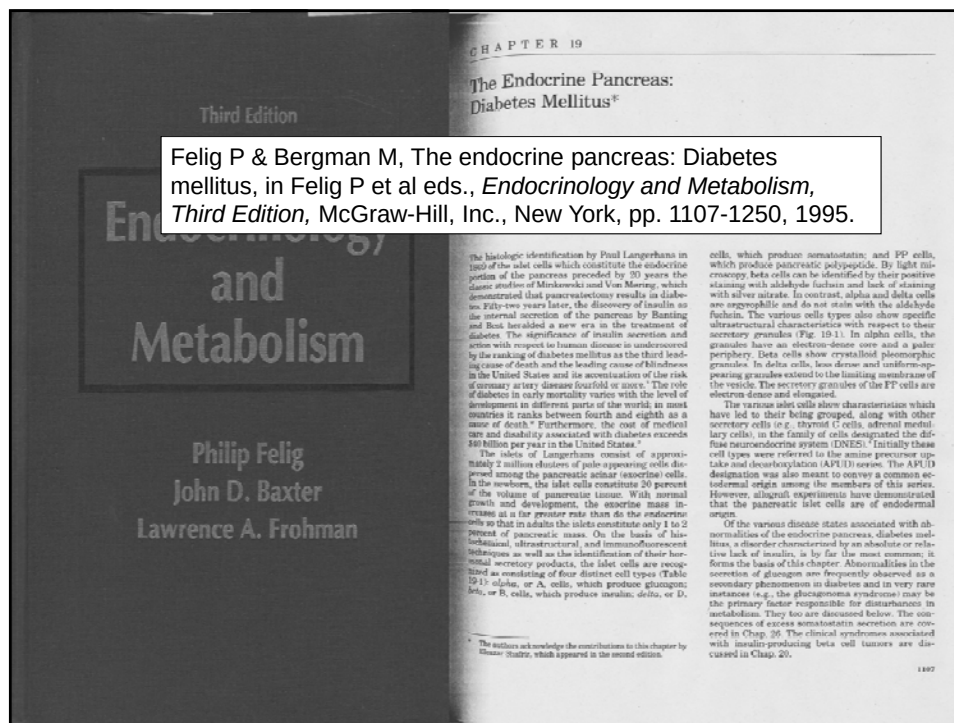
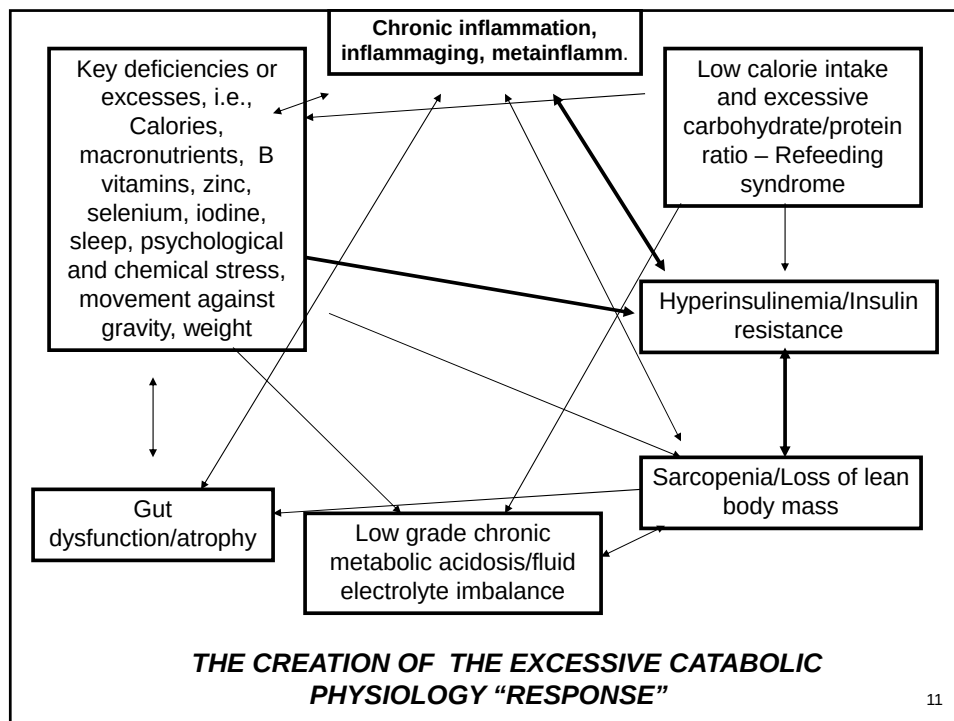
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Entry Level Clinical Nutrition:

A new model of functional
medicine that incorporates
allostatic load and the “chronic”
acute phase response

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- **“Insulin is the primary factor which controls the storage and metabolism of ingested metabolic fuels. After a meal, secretion of insulin facilitates the uptake, utilization, and storage of glucose, fat, and amino acids.”**
- **“Conversely, a reduction in the circulating insulin concentration leads to mobilization of endogenous fuels and reduced uptake of ingested nutrients.”**
- **“The action of insulin involves all three major metabolic fuels – carbohydrate, protein, and fat – and occurs in three principal tissues: liver, muscle, and adipose tissue.”**

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“In each of these tissues there are anticatabolic as well as anabolic effects of insulin which act to reinforce each other.”

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TABLE 19-4 Insulin Action on Liver, Adipose Tissue, and Muscle

	Liver	Adipose Tissue	Muscle
Anticatabolic effects	↓ Glycogenolysis ↓ Gluconeogenesis	↓ Lipolysis	↓ Proteolysis ↓ Amino acid output
Anabolic effects	↓ Ketogenesis ↑ Glycogen synthesis ↑ Fatty acid synthesis	↑ Fatty acid uptake, synthesis, and esterification	↑ Amino acid uptake ↑ Protein synthesis ↑ Glycogen synthesis

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SECOND EDITION
Amino Acids and Proteins
for the Athlete
The Anabolic Edge

DiPasquale M. Proteins and amino acids, in *Amino Acids and Proteins for the Athlete: The Anabolic Edge, Second Edition*, CRC Press, Boca Raton, 1997, pp. 1-10.

“Insulin, beta-adrenergic agonists, androgen/anabolic steroids, and growth hormone increase cellular hydration by promoting the cellular accumulation of several ions or minerals (including potassium, sodium, and chloride...)”

Mauro G. Di Pasquale

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Magnesium and Insulin Resistance

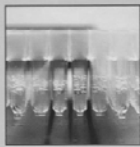
“In a recent study, the cellular uptake of Mg^{++} , which is normally stimulated by insulin, was shown to be attenuated in diabetics. There is also evidence that magnesium deficiency itself produces insulin resistance in normal subjects.”

Tosiello L. Hypomagnesemia and diabetes mellitus, Arch Intern Med, Vol. 156, pp. 1143-1148, June 10, 1996.

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LABORATORY EVALUATIONS

FOR INTEGRATIVE AND FUNCTIONAL MEDICINE



Miller MN et al. Hormones, in Lord RS & Bralley JA. Eds., Laboratory Evaluations for Integrative and Functional Medicine, 2nd Edition, Metamatrix Institute, Duluth GA, 2008, pp. 545-586

J. ALEXANDER BRALLEY
EDITORS

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“Insulin is an anabolic hormone that functions to increase growth, DNA synthesis and cell replication.”

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Molecular basis of insulin action. [Drug News Perspect. 2007] - PubMed result Page 1 of 1

PubMed
U.S. National Library of Medicine
National Institutes of Health

Display Settings Abstract

Drug News Perspect. 2007 Oct;20(8):527-31.

Molecular basis of insulin action.
Gonzalez-Sanchez JL, Serrano-Rios M.
Department of Internal Medicine II, Hospital Clinico San Carlos, Madrid, Spain.

Abstract
Insulin is the main anabolic and anticatabolic hormone in mammals. The stimulatory effect of insulin on glucose uptake in muscle and adipose tissue is a consequence of the rapid translocation of GLUT4 glucose transporters from an intracellular pool to the cell surface.

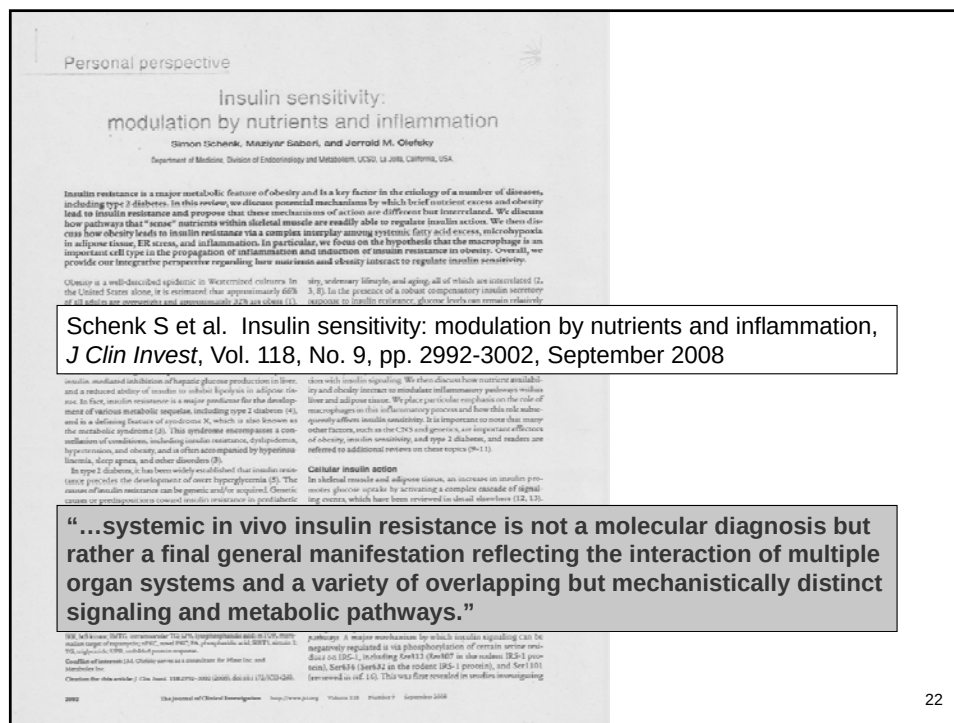
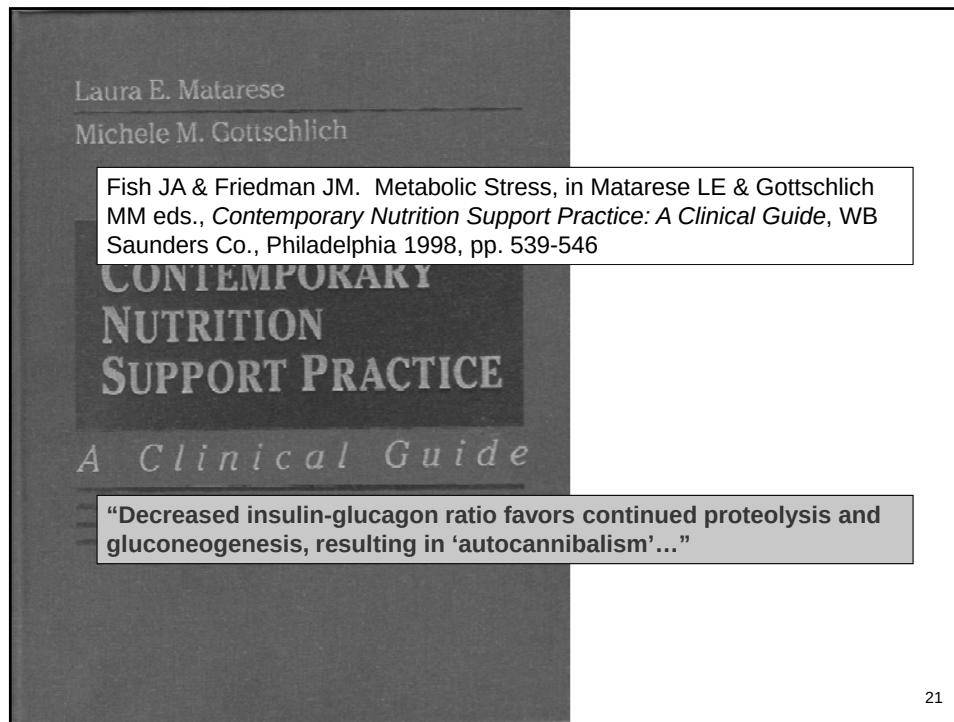
Gonzalez-Sanchez JL & Serrano-Rios M. Molecular basis of insulin action, *Drug News Perspect*, Vol. 20, No. 8, pp. 527-31, October 2007

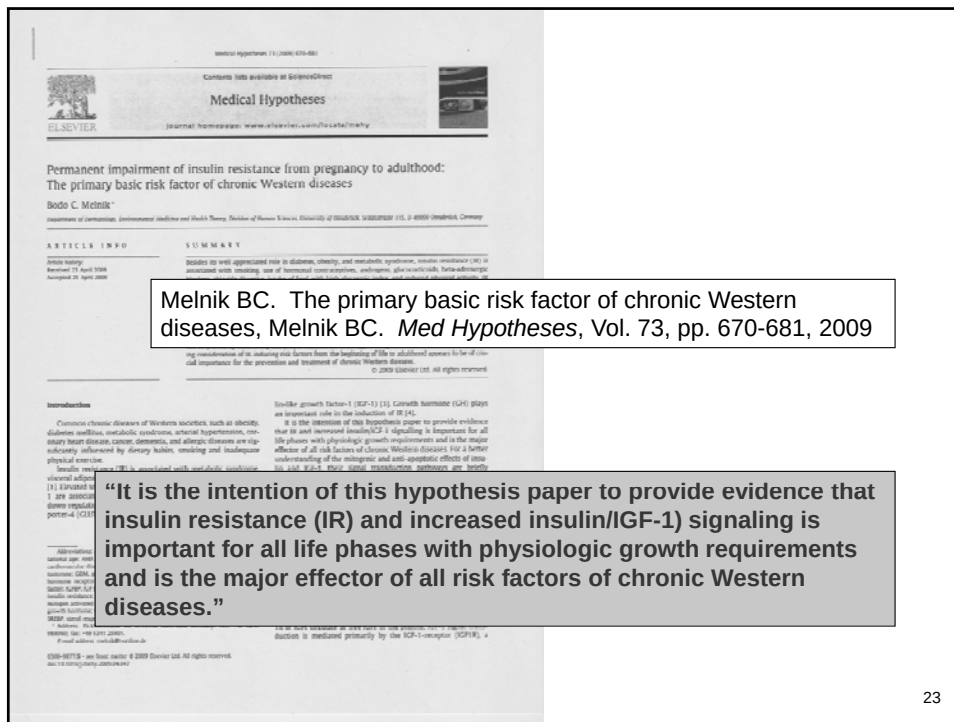
Publication Types, MeSH Terms, Substances
LinkOut - more resources

“Insulin is the main anabolic and anticatabolic hormone in mammals.”

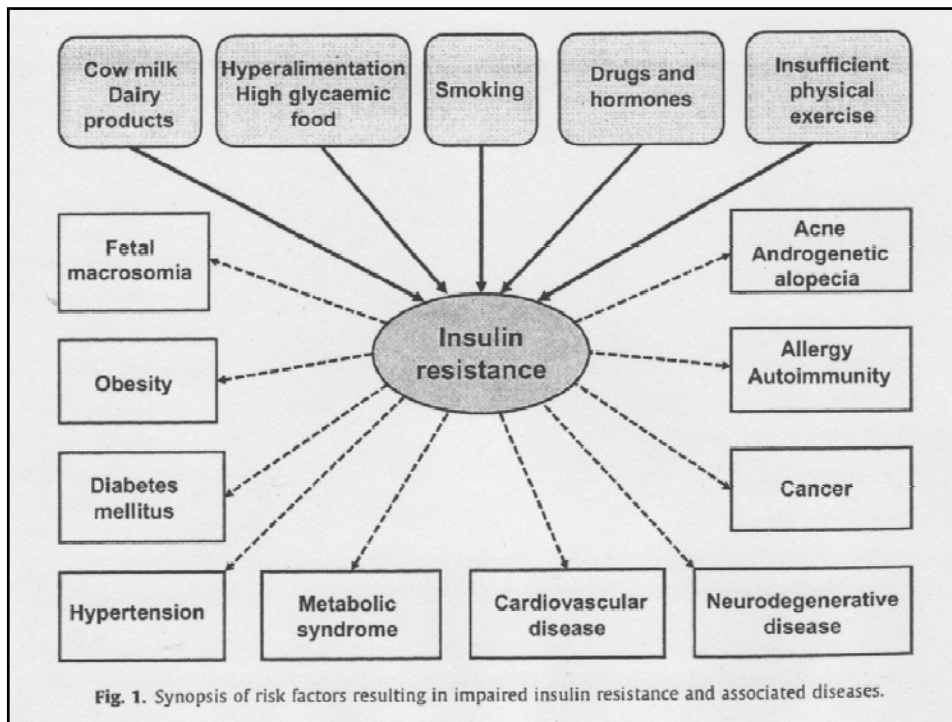
<http://www.ncbi.nlm.nih.gov/pubmed/18080040> 8/26/2010

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- “It will be shown that Western life style risk factors like obesity, consumption of cow milk and dairy products, hyperalimentation, increased intake of food with high glycaemic index, use of hormonal contraceptives, androgen abuse, common drugs like beta-adrenergic blockers and glucocorticoids, smoking, and inadequate physical exercise altogether permanently induce *pathologic IR* beginning already during pregnancy and fetal life persisting into adulthood.”
- “IR causes hyperinsulinaemia and elevated serum levels of IGF-1.”
- “Both hormones are potent mitogens, stimulate growth, cell proliferation, and exert anti-apoptotic activity, which have been correlated with the pathophysiology of metabolic disorders, cardiovascular diseases, cancer and neurodegenerative disorders.”

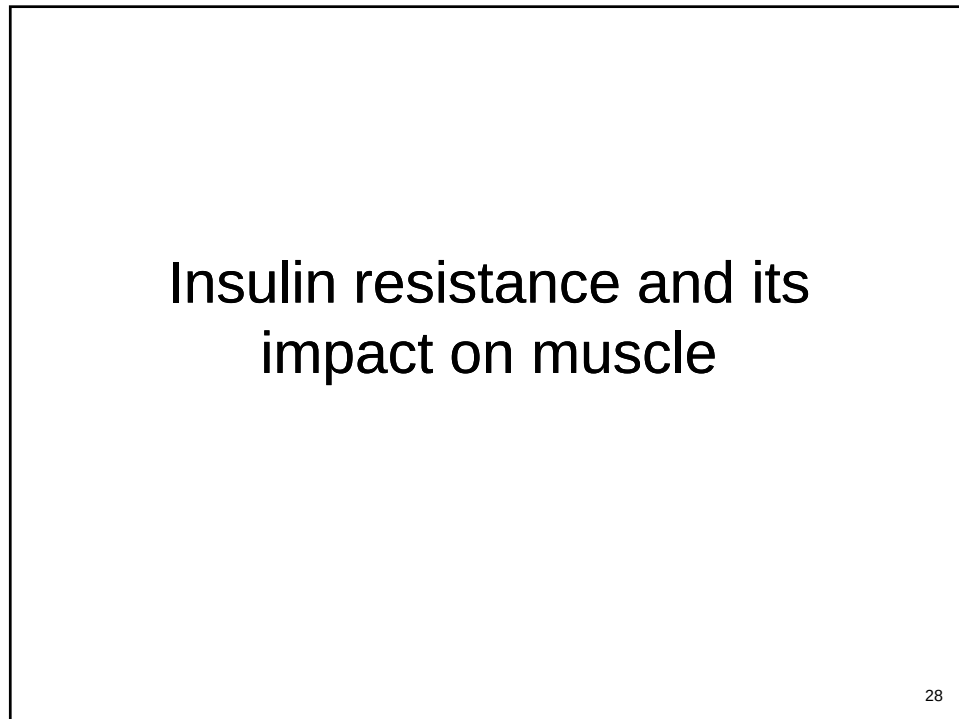
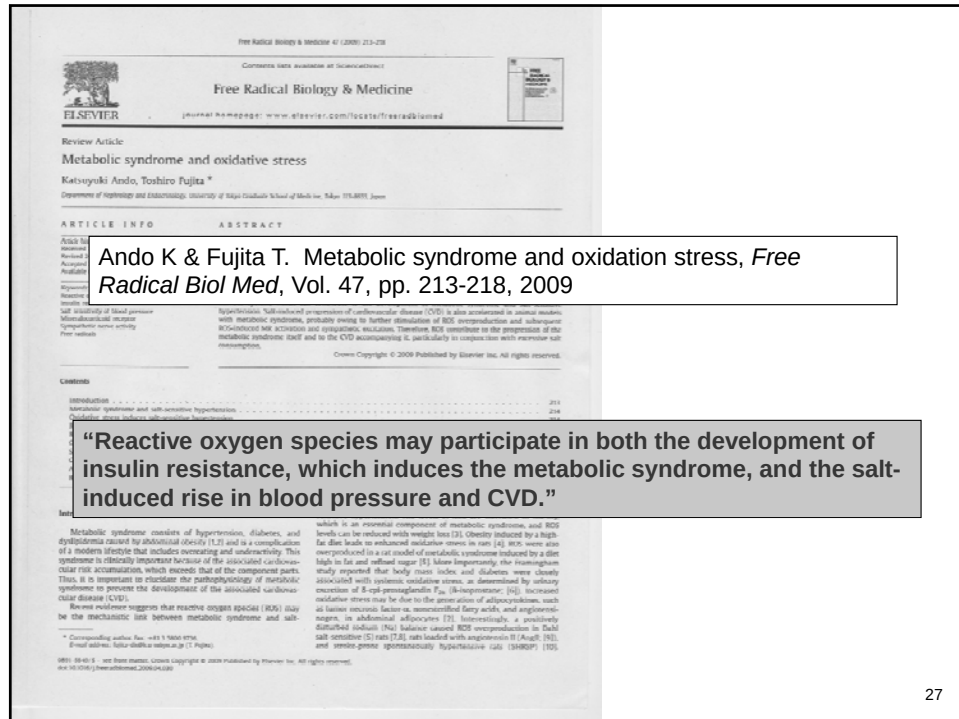


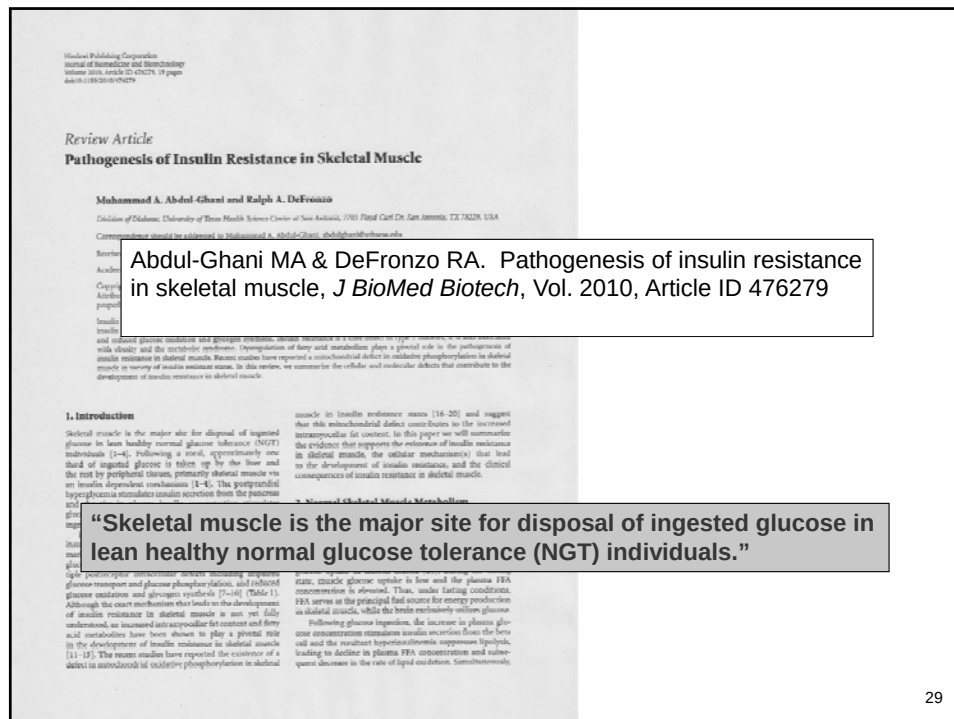
B.C. Melnik / Medical Hypotheses 73 (2009) 670–681

Physiologic insulin resistance		Abnormally impaired insulin resistance	
Fetal growth	IR ↑	IR ↑↑	Gestational diabetes, obesity ← cow milk and dairy intake
Postnatal growth	IR ↑	IR ↑↑	Cow milk based formula • <i>Abnormal programming of insulin-IGF-1-axis</i>
Breast feeding		IR ↑↑	Cow milk, dairy, CH + high GI • <i>Acne, atopic diseases</i>
Prepubertal and pubertal growth	IR ↑	IR ↑↑	Smoking, hormonal contraceptives, androgens
Adolescence		IR ↑↑	Diabetes mellitus, obesity smoking, insufficient exercise, steroids, β-blockers, thiazides • <i>Diabetes, CVD, cancer</i>
Adult life		IR ↑↑	Hormonal replacement and other adult risk factors • <i>Early onset of neurodegenerative disease</i>
Menopause; Climacterium virile		IR ↑↑	
Senescence			

physiologic insulin resistance during normal growth phases (left panel) and abnormally impaired insulin resistance during adult life (right panel). CH = carbohydrate, CVD = cardiovascular disease.

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- **“Following a meal, approximately one third of ingested glucose is taken up by the liver and the rest by peripheral tissues, primarily skeletal muscle via an insulin dependent mechanism.”**
- **“The postprandial hyperglycemia stimulates insulin secretion from the pancreas and the rise in plasma insulin concentration stimulates glucose uptake in skeletal muscle leading to the disposal of ingested glucose.”**

“In insulin resistance states, such as type 2 diabetes mellitus (T2DM) and obesity, insulin-stimulated glucose disposal in skeletal muscle is markedly impaired.”

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- **“Although the exact mechanism that leads to the development of insulin resistance in skeletal muscle is not yet fully understood, an increased intramyocellular fat content and fatty acid metabolites have been shown to play a pivotal in the development of insulin resistance in skeletal muscle.”**
- **“The recent studies have reported the existence of a defect in mitochondrial oxidative phosphorylation in skeletal muscle in insulin resistance states and suggest that this mitochondrial defect contributes to the increased intramyocellular fat content.”**

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How muscle handles energy under normal circumstances

- “Skeletal muscle utilizes both glucose and free fatty acid (FFA) as fuel sources for energy production.”
- During the postabsorptive state, the plasma insulin concentration is low. Since the plasma insulin concentration is the principal factor that restrains lipolysis in adipocytes and stimulates glucose uptake in skeletal muscle, during the fasting state, muscle glucose uptake is low and the plasma FFA concentration is elevated.”

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“Thus, under fasting conditions, FFA serves as the principal fuel source for energy production in skeletal muscle, while the brain exclusively utilizes glucose.”

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What happens with food ingestion?

- **“Following glucose ingestion, the increase in plasma glucose concentration stimulates insulin secretion from the beta cell and the resultant hyperinsulinemia suppresses lipolysis, leading to decline in plasma FFA concentration and subsequent decrease in the rate of lipid oxidation.”**
- **“Simultaneously, insulin stimulates glucose uptake in skeletal muscle, and the increased glucose flux into skeletal muscle, together with the activation of key enzymes in glucose metabolism by insulin, leads to a marked increase in muscle glucose oxidation.”**

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What is the net result?

- **“Thus, under postprandial conditions, for example, mixed meal, muscle energy metabolism switches from predominant oxidation of fat during the fasting state, to predominant oxidation of glucose.”**
- **“The ability of skeletal muscle to switch from fat oxidation during the fasted state to glucose oxidation during the postprandial state has been referred to as metabolic flexibility.”**

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What happens with insulin resistance?

- **“...approximately 80% of total body glucose uptake occurs in skeletal muscle.”**
- **“...insulin resistance in skeletal muscle in subjects with T2DM is manifested, not only by a reduction in the magnitude of insulin action, but also by delayed onset of insulin action to stimulate glucose uptake.”**

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What happens with insulin resistance?

“Insulin resistance in skeletal muscle is manifested long before the hyperglycemia becomes evident.”

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Insulin resistance and other key metabolic imbalances discussed in ELCN

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Obesity

- **“...obese normal glucose tolerance (NGT) subjects without a family history of T2DM and individuals with essential hypertension and ischemic heart disease also have a 35-50% decrease in whole body insulin-mediated glucose disposal.**

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Other metabolic imbalances

- **“Insulin resistance in skeletal muscle also has been reported in association with the normal aging process, dyslipidemia (increased plasma triglyceride/decreased HDL cholesterol, and in association with many disease states including polycystic ovary syndrome (PCOs), chronic kidney failure, heart failure, myotonic dystrophy, and lipodystrophy.”**

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- **“In addition, insulin resistance develops in acute severe illnesses such as injury and sepsis, perhaps secondary to the acute inflammatory state that prevails.”**
- **“Insulin resistance in skeletal muscle also can develop secondary to pharmacological therapy, for example, glucocorticoids, anti-HIV therapy, and beta blockers.**

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“These studies indicate that although insulin resistance in skeletal muscle is a hallmark of T2DM, muscle insulin resistance and the accompanying insulin resistance syndrome are more widely prevalent and the metabolic and clinical consequences of insulin resistance (e.g., increased cardiovascular risk) affect nondiabetic individuals as well.”

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Insulin resistance and obesity

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- **“Obese NGT subjects display marked skeletal muscle insulin resistance compared to lean age and sex matched individuals, and the severity of muscle insulin resistance is related to the increase in BMI.”**
- **“The mechanism via which obesity causes insulin resistance in skeletal muscle is related to the accumulation of fat in the myocytes.”**

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- **“Obese normal glucose tolerance individuals are characterized by an increase in plasma free fatty acid concentration (FFA).”**
- **“The important role of elevated plasma FFA in the in the pathogenesis of insulin resistance is now well established.”**
- **“Considerable data implicate a causative role for elevated plasma FFA level in insulin resistance in skeletal muscle.”**

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- **“Elevated plasma FFA levels correlate strongly with reduced insulin-stimulated glucose disposal in skeletal muscle.”**
- **“FFAs are stored within adipocytes in the form of triglycerides and serve as an important source of energy during fasting.”**
- **“Insulin is a potent inhibitor of lipolysis and restrains the release of FFAs from adipocytes.”**

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- **“In insulin resistant individuals, for example, nondiabetic obese and lean type 2 diabetic subjects, the ability of insulin to inhibit lipolysis and reduce plasma FFA concentration is markedly impaired, leading to an increased rate of lipolysis and chronic elevation in the plasma FFA concentration.”**
- ***“It is well established that chronically elevated plasma FFA levels cause insulin resistance in skeletal muscle.”***

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How do elevations in FFA create insulin resistance in skeletal muscle?

“Much evidence supports the hypothesis that the lipotoxic action of FFA on skeletal muscle insulin sensitivity is due to an increase in the intramyocellular fat content...”

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Is it the fat per se or the toxic metabolites?

- **“These observations collectively indicate that muscle triglyceride (which is metabolically inert) is not directly involved in determining insulin sensitivity but rather represents a marker of imbalance between lipid supply and lipid oxidation in skeletal muscle, while increases in intramyocellular fatty acid acetyl CoA (FACoA) and other lipotoxic metabolites (DAG, ceramide) have a more direct role in the development of skeletal muscle insulin resistance.”**

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Mitochondrial function and insulin resistance in muscle

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- **“Several studies have reported decreased fat oxidation in skeletal muscle, independent of the plasma FFA concentration.”**
- **“Collectively, these studies indicate the existence of an intrinsic defect in mitochondrial capacity to oxidize fat in obesity and T2DM.”**

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Is this reduced mitochondrial activity caused by a decrease in the amount of mitochondria?

- **“...insulin resistance, caused by physiological elevation in plasma FFA concentration in lean healthy individuals, was not associated with a significant change in mitochondrial density in skeletal muscle.”**

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Is the mitochondrial defect in muscle caused by FFA induced insulin resistance reversible?

- **“...several lines of evidence indicate that the mitochondrial defect associated with insulin resistance is reversible, at least in part:”**

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- **(i) modest weight reduction (~10% of body weight), produced by dieting and increased physical activity, reduces insulin resistance and intramyocellular lipid content and these changes are associated with increased fat oxidation in skeletal muscle.”**
- **“Furthermore, the magnitude of increase in fat oxidation following weight loss correlated strongly with the decrease in insulin resistance;”**

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- **(ii) marked weight reduction following bariatric surgery in morbidly obese, severely insulin-resistant subjects completely normalized insulin sensitivity, and correction of the insulin resistance was accompanied by depletion of intramyocellular fat content.”**
- **“Although mitochondrial function was not assessed following weight loss in this latter study, the depletion of intramyocellular fat and normalization of insulin sensitivity suggests a reversible mitochondrial defect in these morbidly obese, insulin-resistant individuals;”**

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- **“(iii) the morphological changes which characterize mitochondria in obese insulin-resistant individuals can be reversed following weight loss and increased physical activity;”**

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- **“(iv) the improvement in insulin sensitivity following exercise is associated with improved muscle oxidative capacity and increases in both mitochondrial density and activity.”**

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**Summary:
Mitochondrial function,
increased FFA influx into
muscle, and muscle insulin
resistance**

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- **“In summary, it can be concluded that both decreased mitochondrial fat oxidation and increased FFA influx into skeletal muscle take place during insulin resistance state.”**
- **“If the rate of fat supply exceeds the demand for fat oxidation, the muscle redirects the fat entering the cell toward triglyceride synthesis leading to increased intramyocellular lipid content.”**
- **“In contrast if fat oxidation exceeds the rate of fat supply, all fat entering the muscle will be directed to fat oxidation and now fat will accumulate in the muscle.” Thus, the intramyocellular lipid content in skeletal muscle reflects the dynamic balance between the demand for fat oxidation and fat supply to the muscle.”**

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“Thus, the intramyocellular lipid content in skeletal muscle reflects the dynamic balance between the demand for fat oxidation and fat supply to the muscle.”

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**Glycogen synthesis and
insulin resistance**

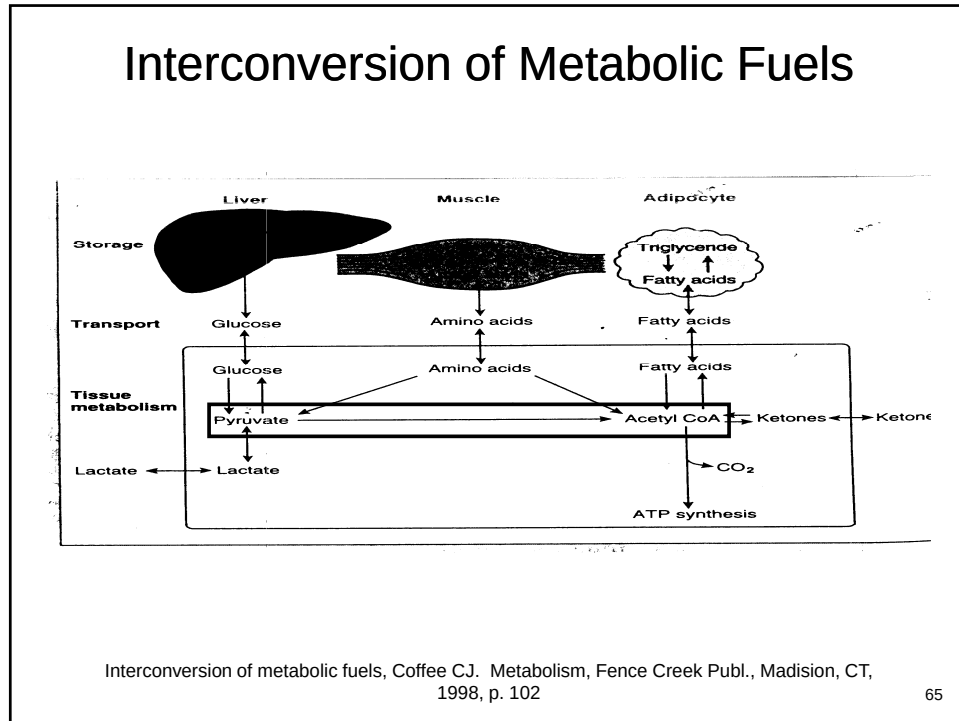
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- **“Under anabolic conditions, insulin augments glycogen synthesis by simultaneously activating glycogen synthase and inhibiting glycogen phosphorylase.”**
- **“Impaired insulin-stimulated glycogen synthesis is a characteristic finding in all insulin-resistant states.”**
- **Obese, impaired glucose tolerance, and diabetic subjects have severe impairment of insulin-stimulated glycogen synthase that accounts for the majority of the defect in insulin-mediated whole-body glucose disposal.”**

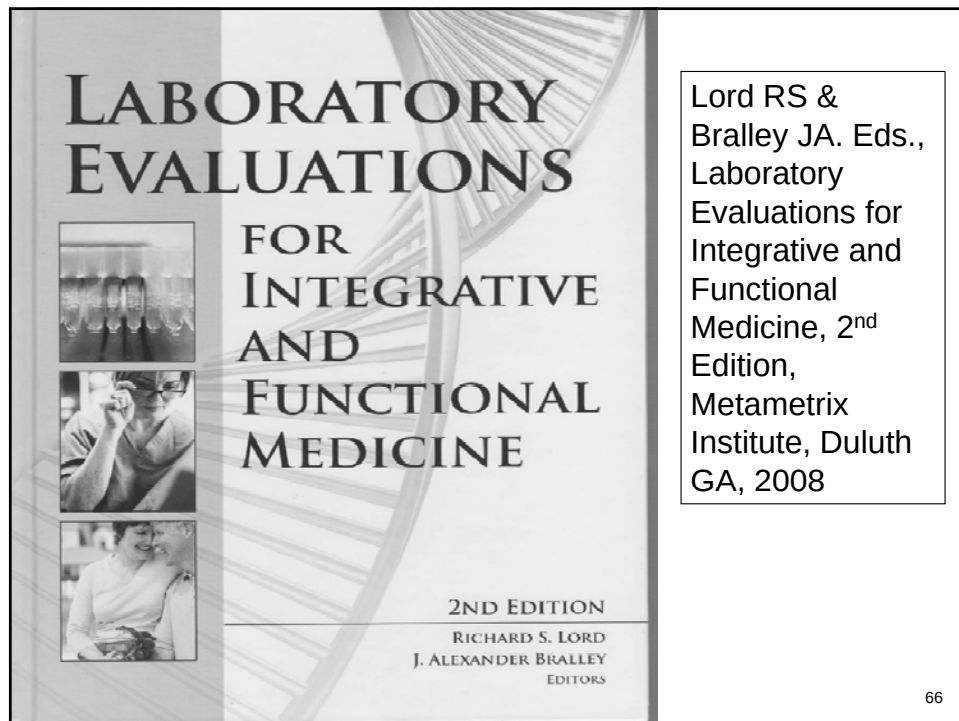
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**Conversion of pyruvate to
acetyl CoA via the pyruvate
dehydrogenase pathway**

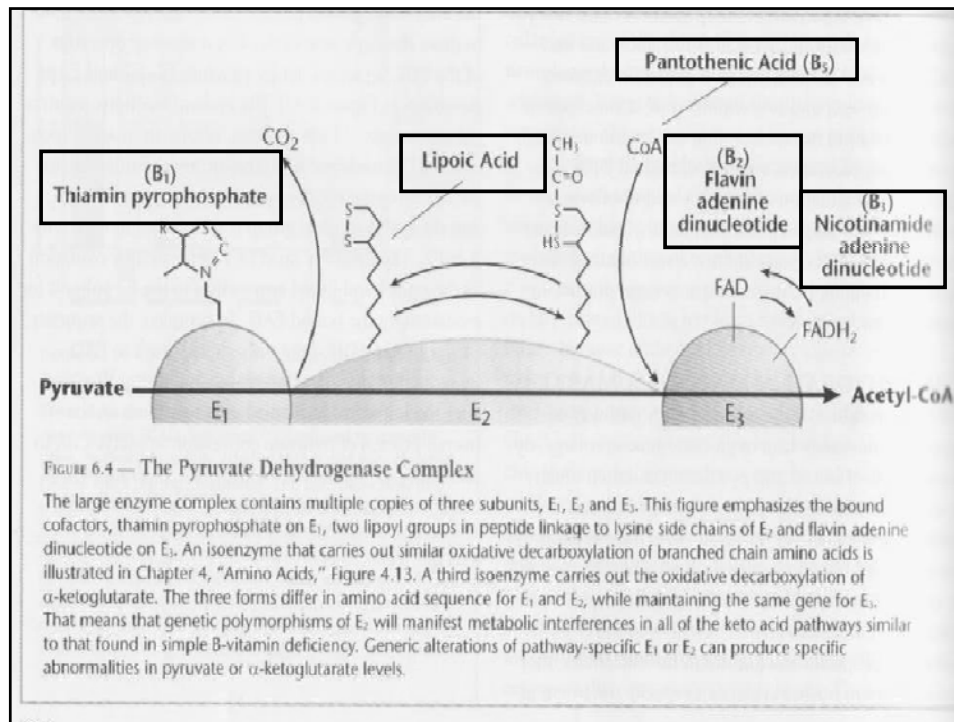
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- **“Obesity and type 2 diabetes mellitus are associated with accelerated FFA turnover and oxidation, which would be expected, according to the Randle cycle, to inhibit PDH activity and consequently glucose oxidation.”**
- **“Therefore, it is likely that the observed defects in glucose oxidation and PDH activity are acquired secondary to increased FFA oxidation and feedback inhibition of PDH...”**

Key issues in optimizing insulin metabolism

- Optimal inflammatory activity – Excessive inflammation can contribute to insulin resistance.
- Optimal levels of cortisol – Excessive levels of glucocorticoids can contribute to insulin resistance.

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Key issues in optimizing insulin metabolism

- Optimal levels of body fat – Obesity can lead to increases in plasma free fatty acid (FFA) levels. Subsequently, increases in FFA can lead to incorporation of FFA in muscle, which is very similar to the “marbling” we see in commercial beef. While this “marbling,” or incorporation of FFA in muscle, may be effective at increasing taste and tenderness, it has a decidedly negative effect on optimal muscle function.

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How does increased intramuscular fat adversely affect insulin metabolism?

- It decreases the ability of insulin to bring glucose into muscle.
- It decreases the ability of insulin to reduce lipolysis, thus creating a vicious circle where increased FFA leads to more FFA formation.
- It inhibits optimal mitochondrial activity
- It inhibits glycogen synthesis
- It inhibits conversion of pyruvate to acetyl CoA via the pyruvate dehydrogenase pathway

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Treatment

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Basics, basics, basics!!!

- Diet
- Exercise
- Glycemic formulas containing chromium, vanadium, lipoic acid, etc.
- Address all the other aspects of ELCN – acid/alkaline balance, chronic inflammation, macro- and micronutrient deficiency, gut dysfunction, etc.

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Thank you!!

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