Lessons from Micronutrient Studies in Patients with Glucose Intolerance and Diabetes Mellitus: Chromium and Vanadium

Henry C. Lukaski, Ph.D.

USDA, ARS Grand Forks Human Nutrition Research Center
Grand Forks, ND 58202
Chromium in Glucose Metabolism

Cr\(^{+3}\) facilitates insulin action \textit{in vitro}

\uparrow \text{insulin receptor number in adipocytes}

\uparrow \text{insulin binding at receptors}

Cr\(^{+3}\) supplementation of long-term TPN patients improves symptoms of glucose intolerance
Chromium and Glucose/Insulin: Hypothesis

- Dietary Cr intake is low
- Stressors promote acute Cr loss
- Exercise
- Infection
- Pharmaceuticals
Responses to Chromium Supplementation

Glucose mg/dL

Hyper Glycemic
Hypo Glycemic
Control
Diabetic

Placebo
600µg/d

Normal values

Chromium Supplementation in Type II Diabetes

180 adults in Beijing, China (35-65 y)
BMI: 24-25 kg/m²
Double-blind, placebo-controlled design
Maintain medication* use, usual diet and life style
Randomized: placebo, 200, 1000 µg Cr as CrPic
Fasting and OGTT glucose and insulin

*Sulfonylureas, metformin, insulin, traditional meds

Anderson et al, Diabetes 46:1786, 1997
Effects of Chromium on Fasting Serum Glucose

Anderson et al, Diabetes 46:1786, 1997
Effects of Chromium on Fasting Insulin

Anderson et al, Diabetes 46:1786, 1997
Effects of Chromium on Hemoglobin A1C

Anderson et al, Diabetes 46:1786, 1997
Reduced Fasting Glucose with Cr Supplementation

Improved Insulin Sensitivity with Cr Supplementation

Reported Beneficial Effects of Chromium Supplementation

Steroid-induced diabetes

- 47 out of 50 patients improved with 600 µg Cr as CrPic for 14 d

Gestational diabetes

- 4 and 8 µg Cr/kg as CrPic for 8 wk decreased fasting insulin, glucose and insulin conc. during OGTT
- With severe glucose intolerance, Cr did not reduce insulin requirement
Cr Supplementation and Human Diabetes: Summary

Doses of Cr > 200 µg/d as CrPicit elicit positive effects
Increased insulin sensitivity
Improved diabetic control
↓ fasting glucose
↓ fasting insulin
↓ HbA1C
No relationship between serum Cr and diabetic control
Activation of Insulin Receptor Activity by Chromium

**Insulin-sensitive cell**
- Insulin receptor (IR) fully activated
- Chromodulin in blood
- Apo chromodulin

**Insulin receptor activated**
- Insulin receptor (IR) activated
- Cr+3-Transferrin
- Apo chromodulin + 4 Cr+3
- K_f ~ 10^{18} m M^{-1}

**Chromodulin loaded with Cr**
- Chromodulin
- Urine
- K_m ~ 250 pM

Adapted from Vincent, J Nutr 130:715, 2000
Proposed Sites of Chromium & Vanadium Action

- **Insulin**
- **Insulin Receptor**
- **α unit**
- **β unit**
- **ATP**
- **Glucose**
- **Glucose Transporter**
- **Protein Synthesis**
- **Lipid Synthesis**
- **Glycogen Synthesis**
- **Growth Gene Expression**

**Phosphorylation Cascades**

**Cr (Insulin binding)**

**Cr, V (↓ PTPase)**

**Cr (↑ Receptor kinase)**

**V (↓ PTPase)**

**PTPase = phosphotyrosyl protein phosphatase**
Vanadium in Glucose Metabolism and Diabetes

V salts, vanadyl (VO$^{+2}$) and vanadate (VO$_3^-$), mimic insulin action.

In vitro, vanadate: $\uparrow$ hexose uptake in muscle & adipocytes, $\uparrow$ lipid and $\uparrow$ glycogen synthesis.

In vivo, vanadate and vanadyl are effective treatments for Type I and II diabetes in rodents.

V improves blood glucose without increasing blood insulin.

Primary action of V is at target tissues.
Vanadium Supplementation in Diabetes

Glucose use - ↑ in NIDDM, no change in IDDM
Non oxidative disposal - ↑ in NIDDM
Hepatic glucose production - no change in NIDDM or IDDM
Insulin requirement - ↓ in IDDM
No significant change in fasting glucose or HbA1C

Sodium metavanadate (NaVO₃; 125 mg or ~ 50 mg V) for 2 wk
Glucose metabolism: 2-step euglycemic, hyperinsulinic clamp

Goldfine et al, J Clin Endocrinol Metab 80: 3311, 1995
Vanadyl Sulfate: Diabetic Control

Goldfine et al, Metabolism 49:400, 2000
Changes in Serum Vanadium with Vanadium Supplementation

Goldfine et al, Metabolism 49: 400, 2000
Serum Vanadium Concentrations

Therapeutic Levels in STZ-diabetic rats

Vanadium, ng / mL

- 25 mg V (VOSO₄)
- 50 mg V (VOSO₄)
- 50 mg V (NaVO₃)
Serum Vanadium Concentrations

PTPase Activity (% control)

Vanadium Concentration (µM)

Human studies

1.5 mg kg

14 d

Rodent studies

100 mg kg

3 d

Particulate

Cytosolic

1

2

7

15

25

50

100

200

100

80

60

40

20

0
Generally ineffective in IDDM

Improve insulin sensitivity

\[ \uparrow \text{glucose use - non oxidative disposal} \]

Improve diabetic control

\[ \downarrow \text{HbA1C (50 & 100 mg/d): 7.8 to 6.8 \%} \]

\[ \downarrow \text{fasting glucose (100 mg/d): 167 to 144 mg/dL} \]

\[ \downarrow \text{total cholesterol (100 mg/d): 204 to 165 mg/dL} \]

\[ \downarrow \text{HDL (100 mg/d): 39 to 31 mg/dL} \]

No relationship between serum V and insulin sensitivity
Cr & V Supplementation in Diabetes

Common mechanism of action: ↓ PTPase

Increased diabetic control in NIDDM

Serum concentration not predictive of efficacy

Inconsistent response among patients

Pharmaceutical doses needed for beneficial effects
Adverse Effects of Cr & V Supplementation

Chromium

*In vitro* evidence of DNA damage

Vanadium

Gastrointestinal intolerance (V doses ≥ 25 mg/d)

Vanadate > vanadyl salts

HDL-cholesterol

“Green tongue”
Cr & V Supplementation: Nutrition or Pharmacology

Chromium
ESADDI: 50 - 200 µg/d
Therapeutic dose: 500 - 1000 µg/d

Vanadium
Postulated requirement: 10 µg/d
Therapeutic dose: 25 - 50 mg/d
Toxic dose: > 10 mg/d