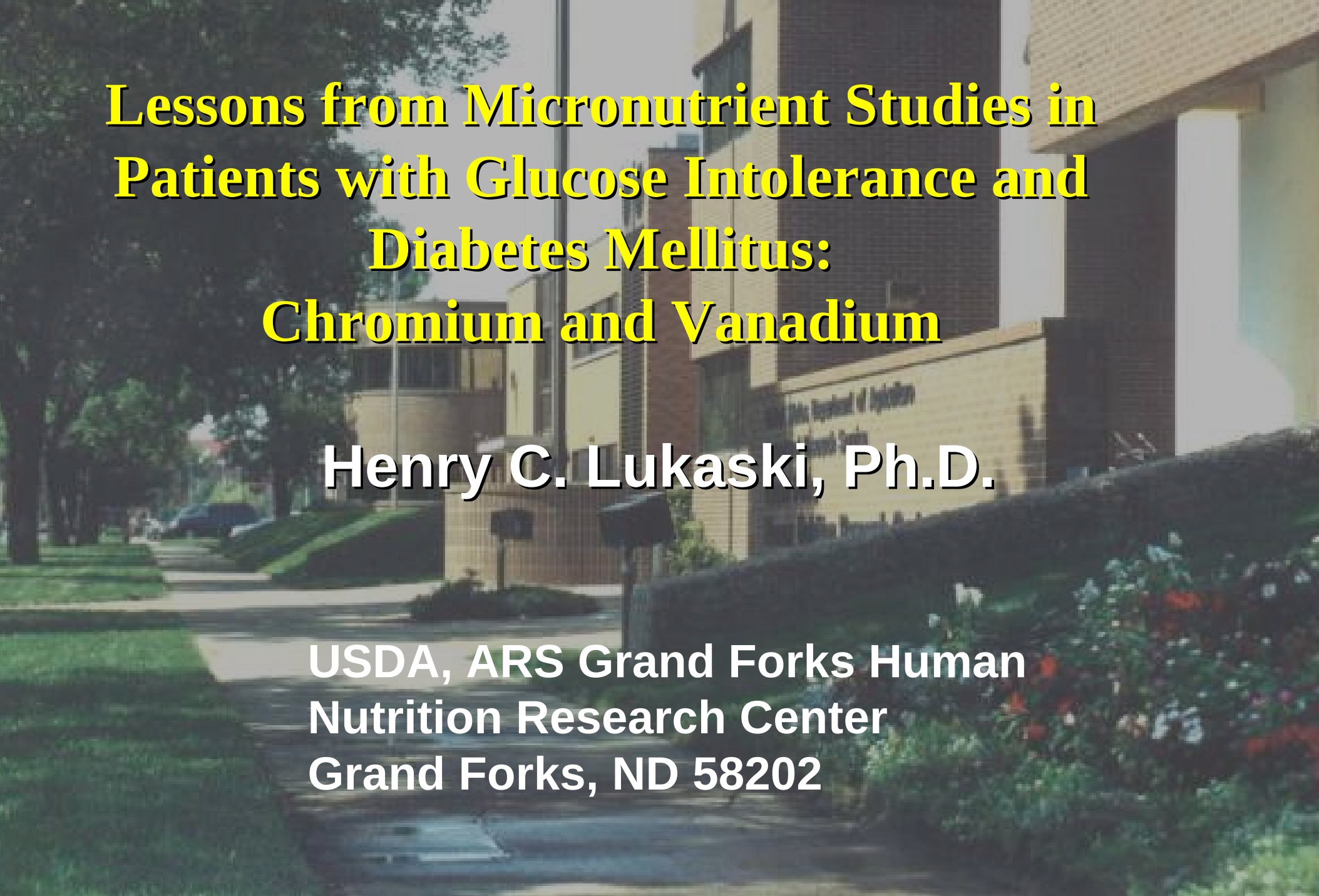

Lessons from Micronutrient Studies in Patients with Glucose Intolerance and Diabetes Mellitus: Chromium and Vanadium

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Chromium in Glucose Metabolism

Cr^{+3} facilitates insulin action *in vitro*

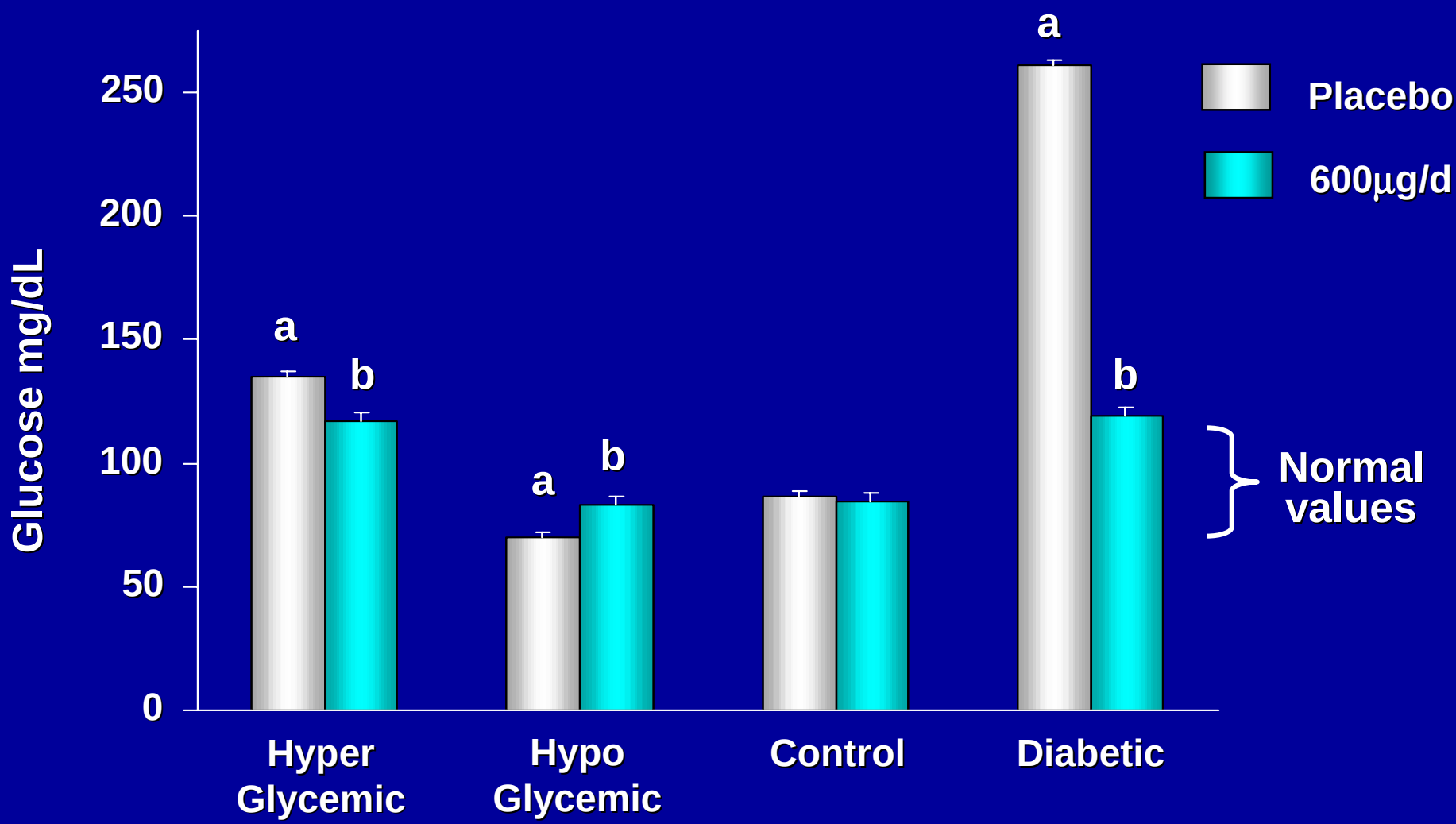
- ↑ insulin receptor number in adipocytes
- ↑ insulin binding at receptors

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



Anderson, J Am Coll Nutr, 16:404, 1997

Chromium Supplementation in Type II Diabetes

180 adults in Beijing, China (35-65 y)

BMI: 24-25 kg/m^2

Double-blind, placebo-controlled design

Maintain medication* use, usual diet and life style

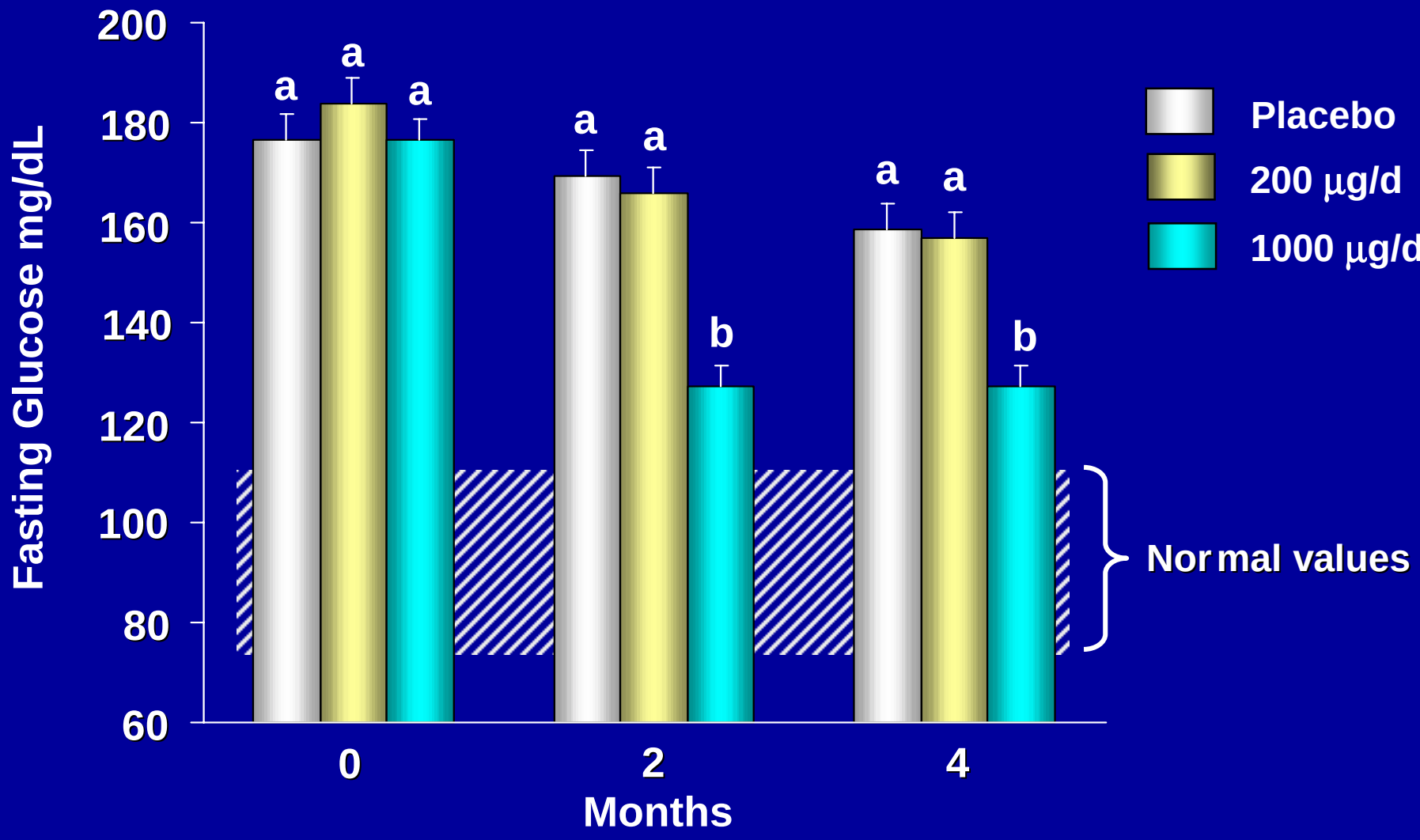
Randomized: placebo, 200, 1000 µg Cr as CrPic

Fasting and OGTT glucose and insulin

*Sulfonylureas, metformin, insulin, traditional meds

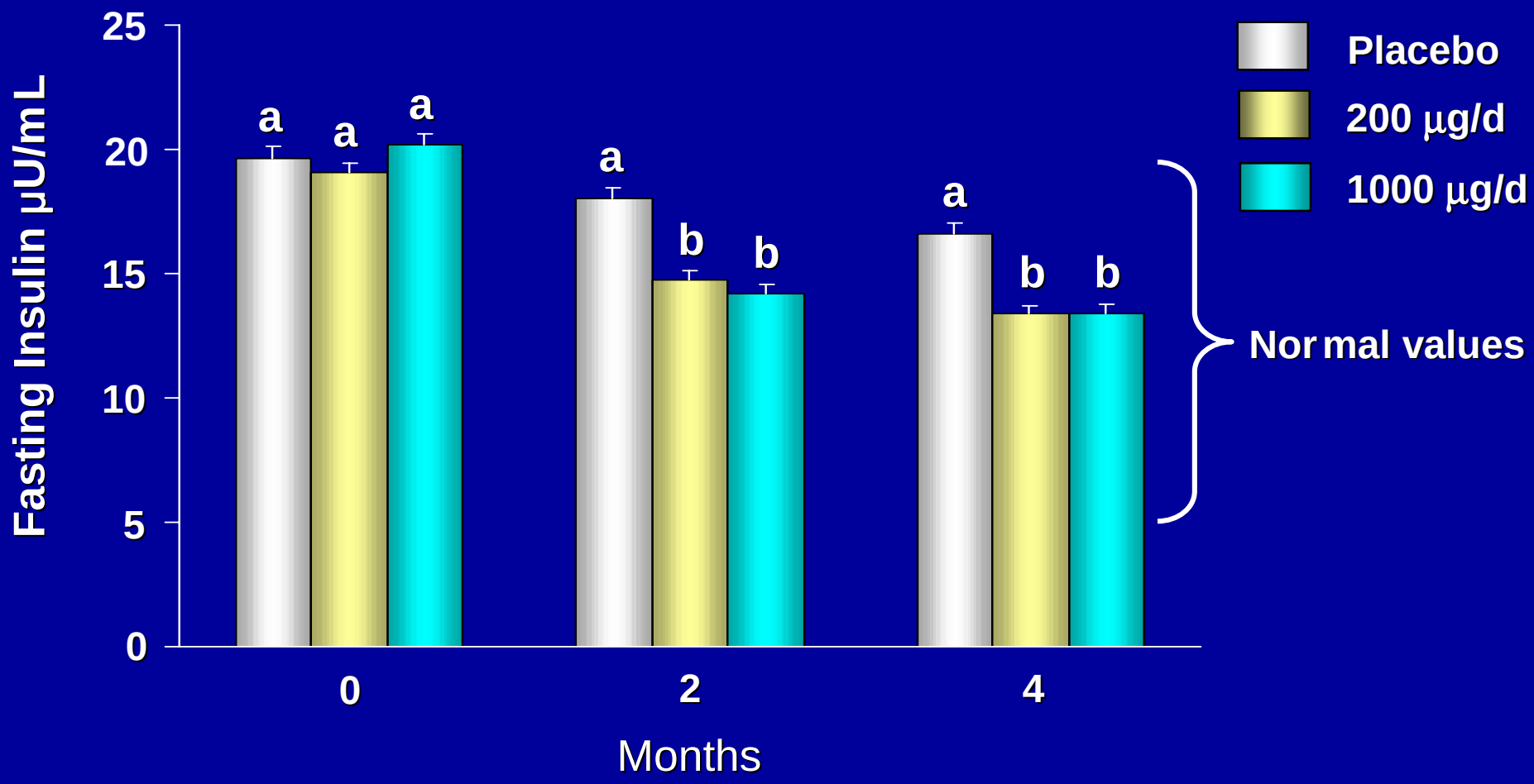
Anderson et al, Diabetes 46:1786, 1997

Effects of Chromium on Fasting Serum Glucose



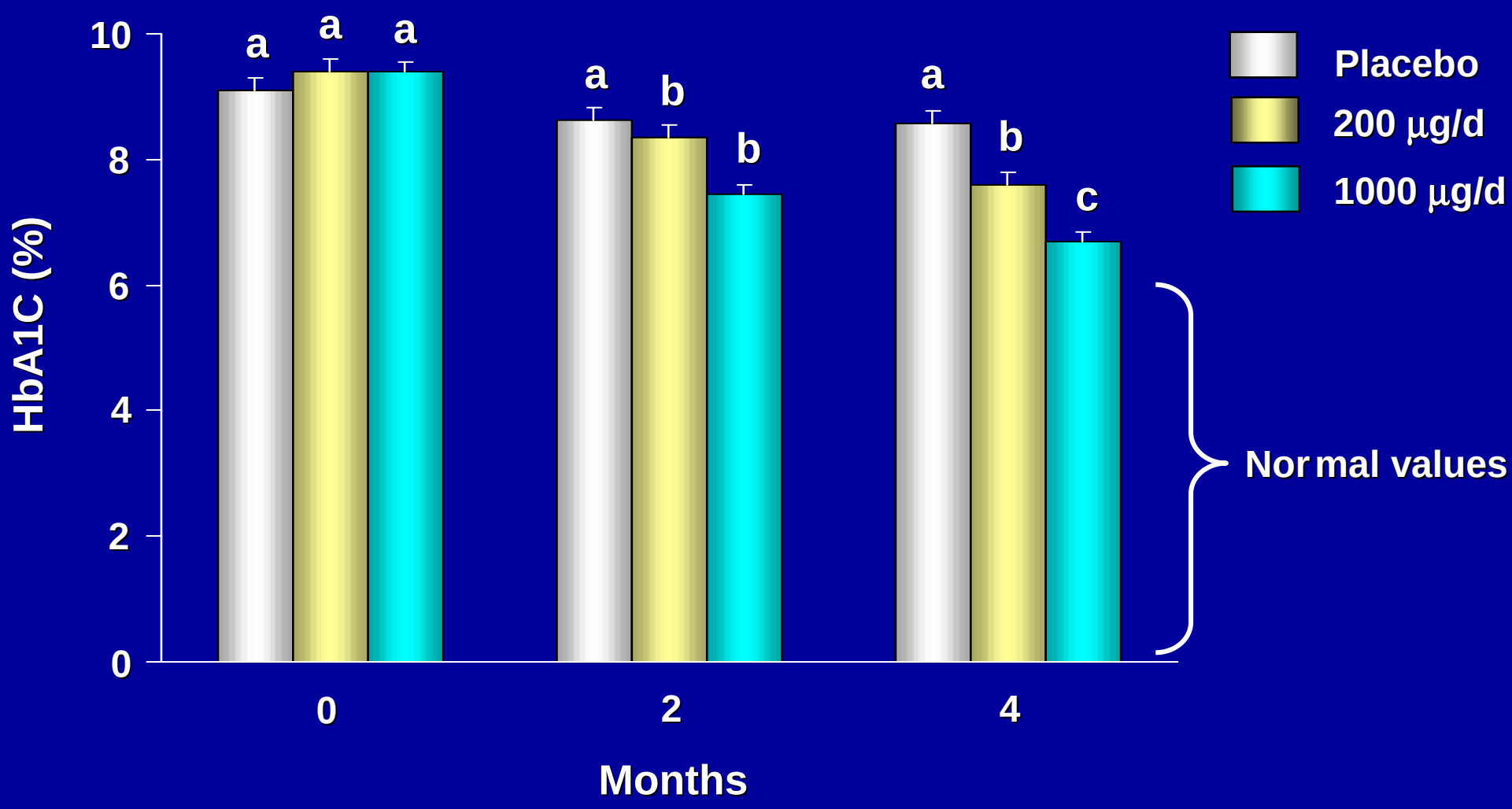
Anderson et al, Diabetes 46:1786, 1997

Effects of Chromium on Fasting Insulin



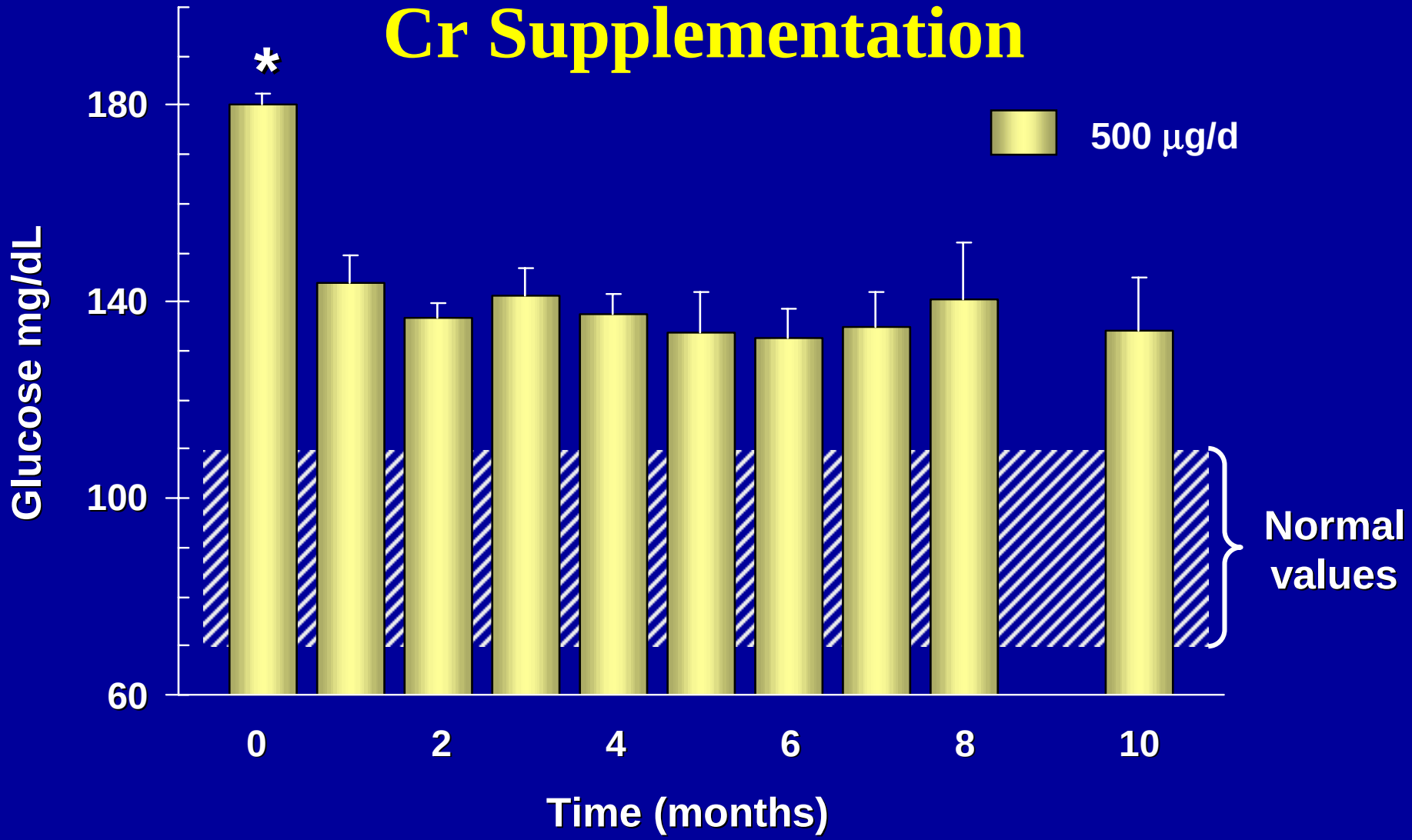
Anderson et al, Diabetes 46:1786, 1997

Effects of Chromium on Hemoglobin A1C



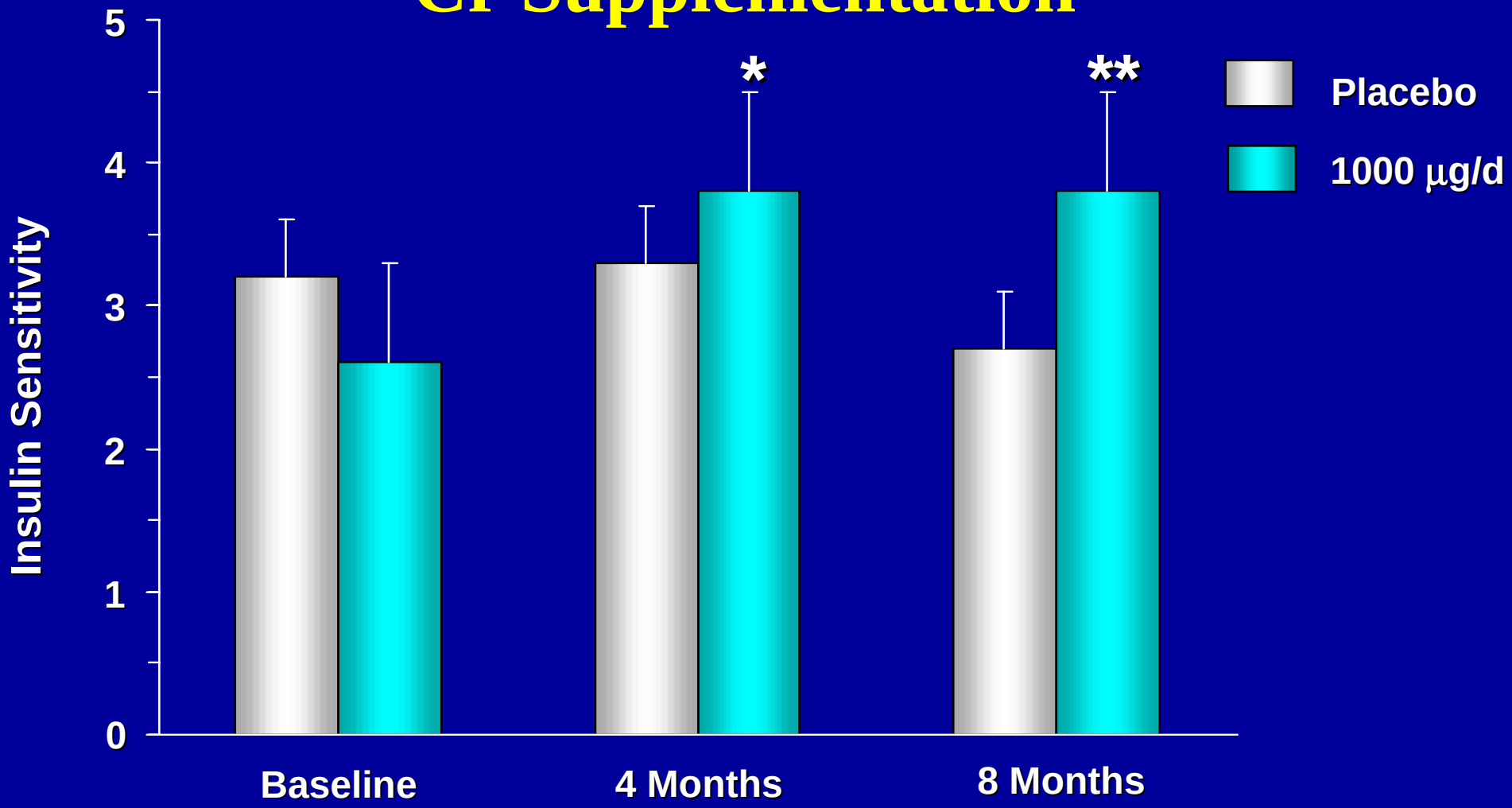
Anderson et al, Diabetes 46:1786, 1997

Reduced Fasting Glucose with Cr Supplementation

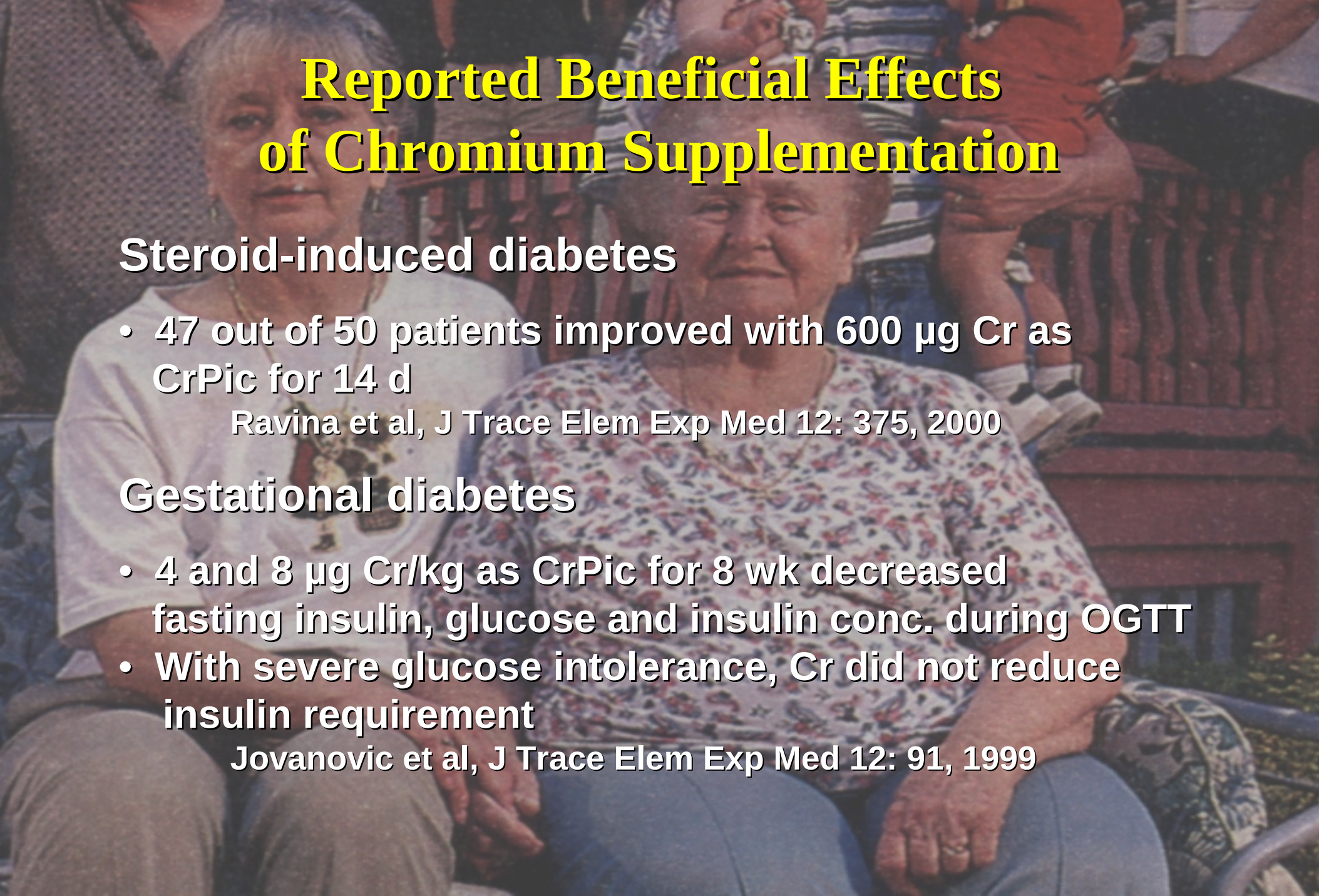


Cheng et al, J Trace Elem Exp Med 12:55 1999

Improved Insulin Sensitivity with Cr Supplementation



Cefalu et al, J Trace Elem Exp Med 12:71, 1999



Reported Beneficial Effects of Chromium Supplementation

Steroid-induced diabetes

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

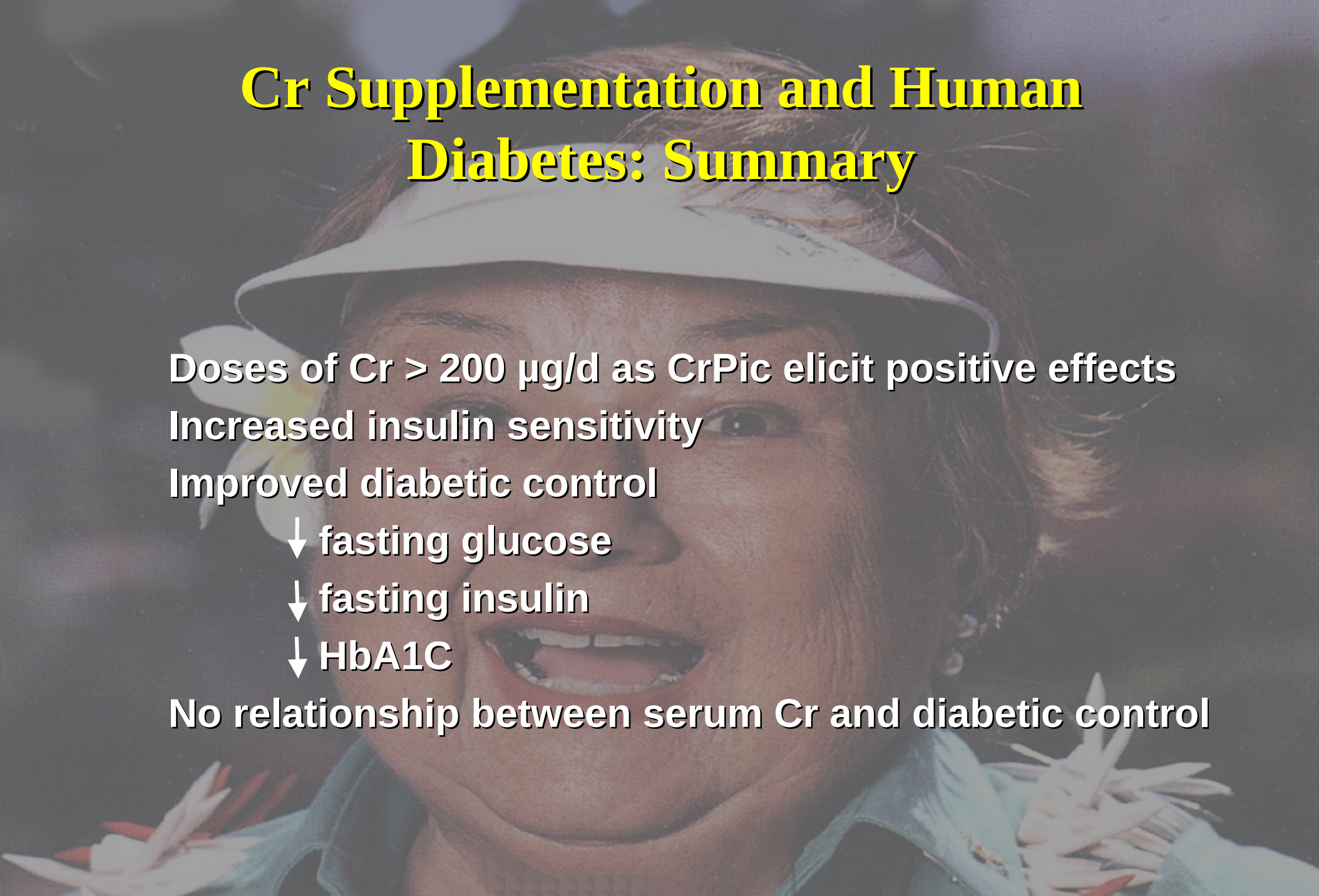
  Ravina et al, J Trace Elem Exp Med 12: 375, 2000

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

  Jovanovic et al, J Trace Elem Exp Med 12: 91, 1999

Cr Supplementation and Human Diabetes: Summary



Doses of Cr > 200 µg/d as CrPic elicit positive effects

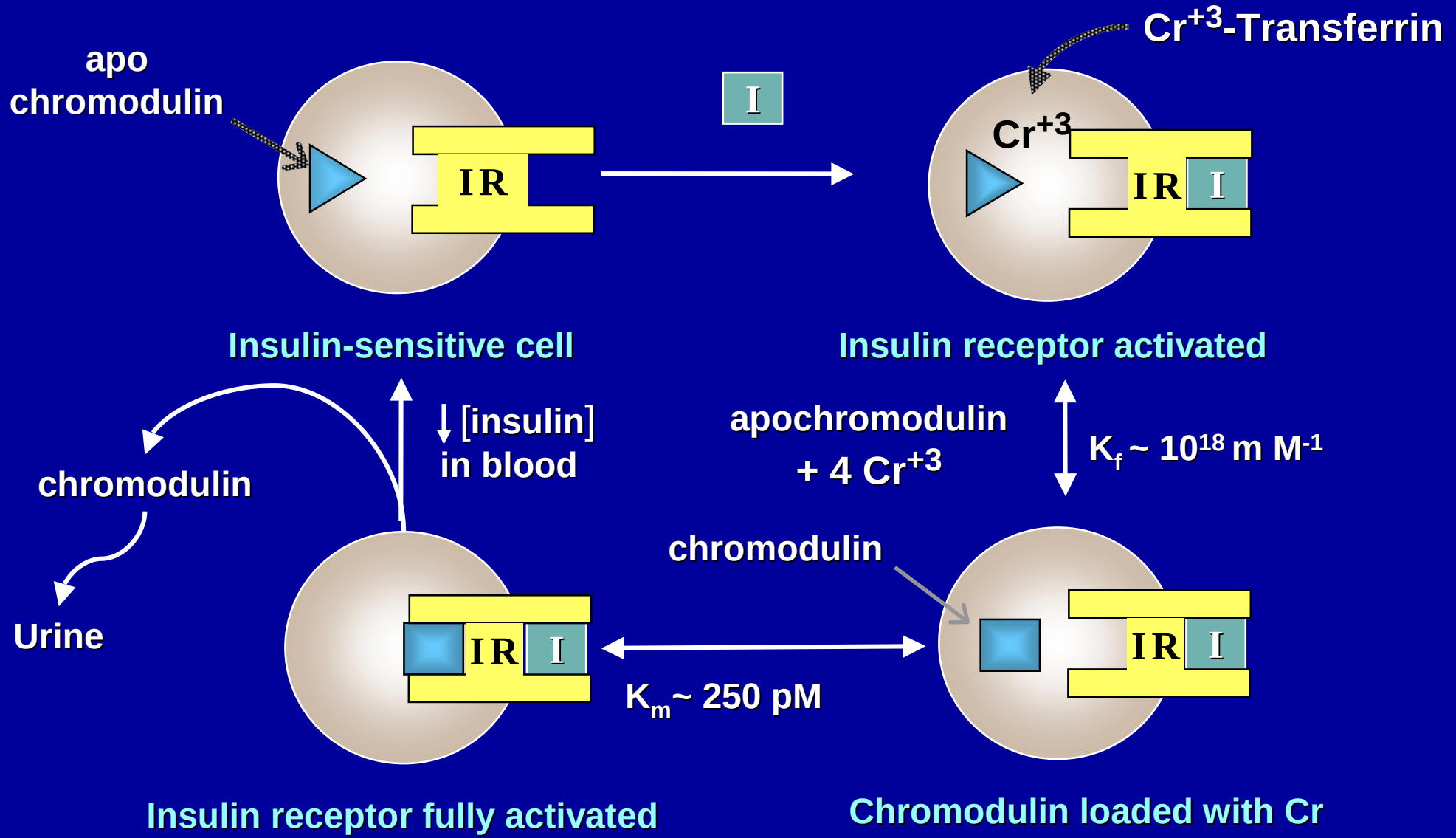
Increased insulin sensitivity

Improved diabetic control

- ↓ fasting glucose
- ↓ fasting insulin
- ↓ HbA1C

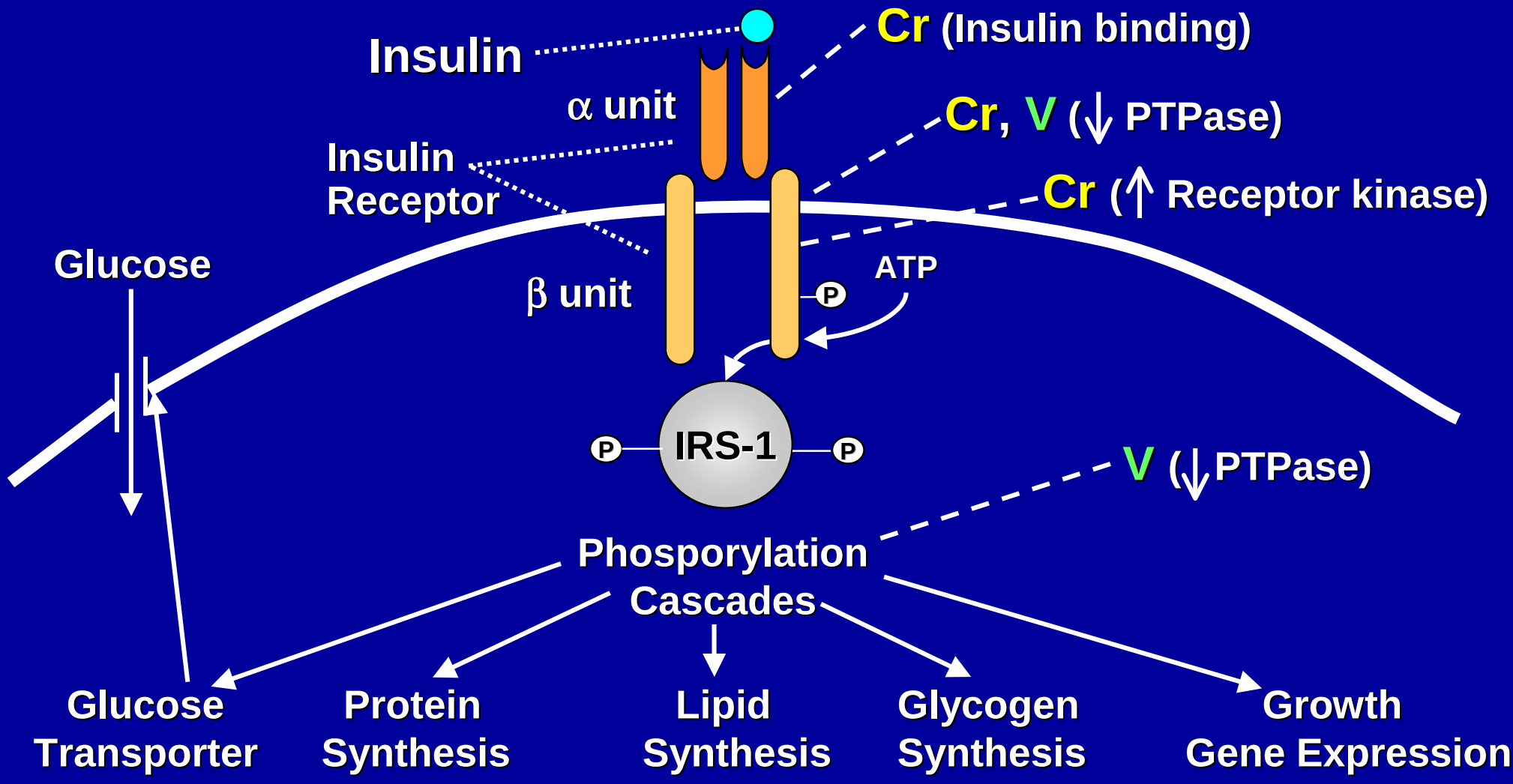
No relationship between serum Cr and diabetic control

Activation of Insulin Receptor Activity by Chromium



Adapted from Vincent, J Nutr 130:715, 2000

Proposed Sites of Chromium & Vanadium Action



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: ↑ hexose uptake in muscle & adipocytes, ↑ lipid and ↑ 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

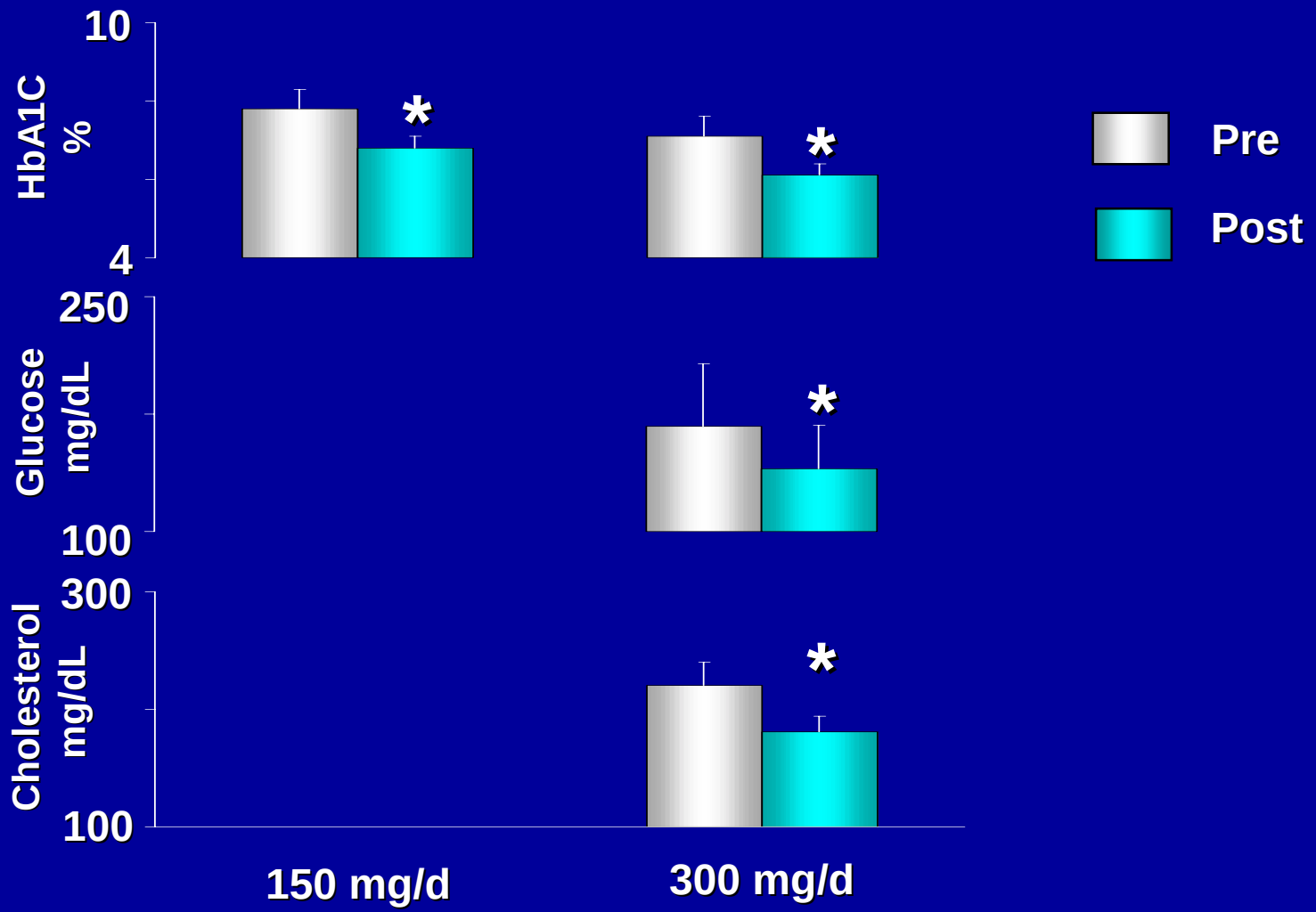
Vanadium Supplementation in Diabetes

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 ($NaVO_3$; 125 mg or ~ 50 mg V) for 2 wk
Glucose metabolism: 2-step euglycemic, hyperinsulinic clamp

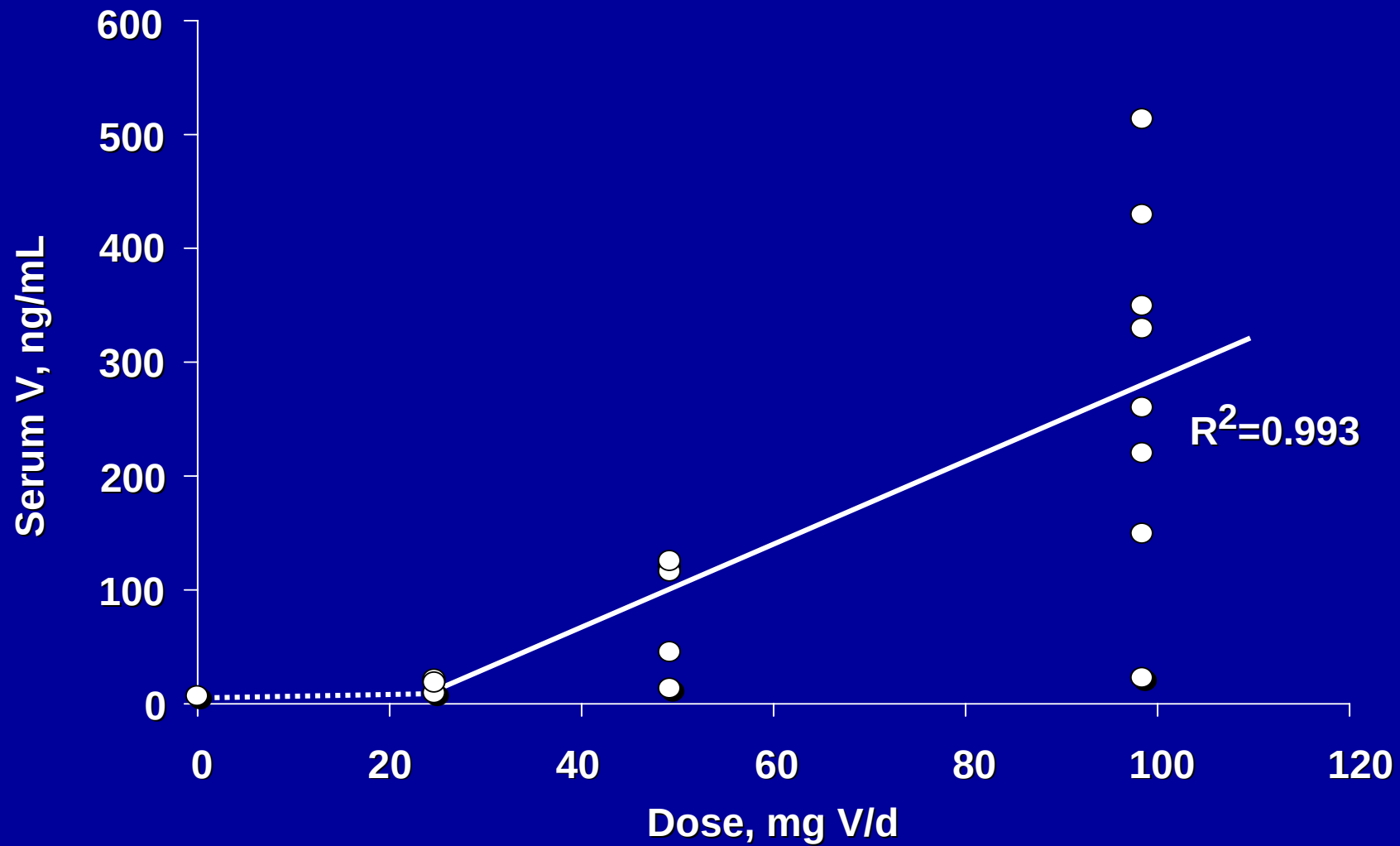
Goldfine et al, J Clin Endocrinol Metab 80: 3311, 1995

Vanadyl Sulfate: Diabetic Control



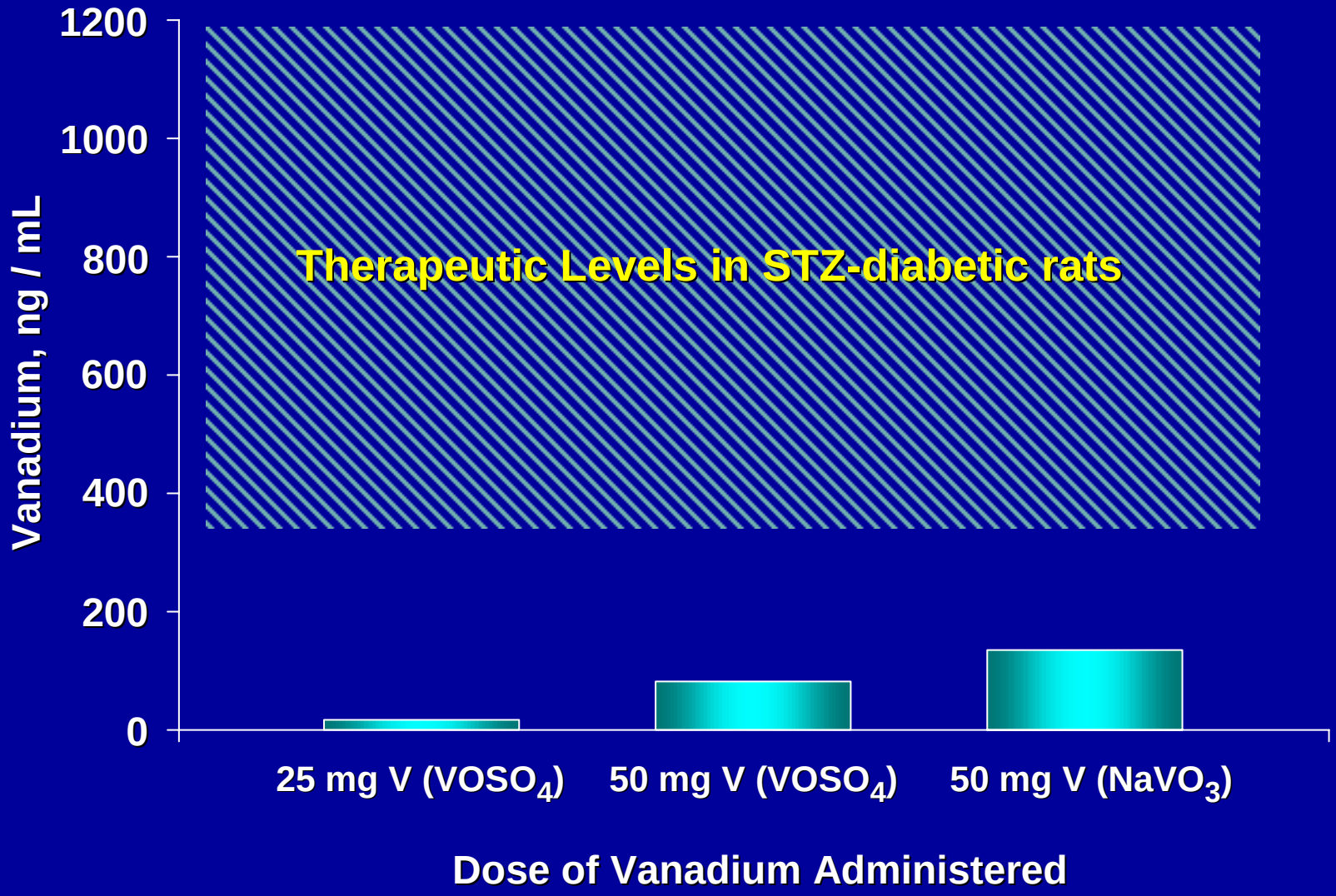
Goldfine et al, Metabolism 49:400, 2000

Changes in Serum Vanadium with Vanadium Supplementation

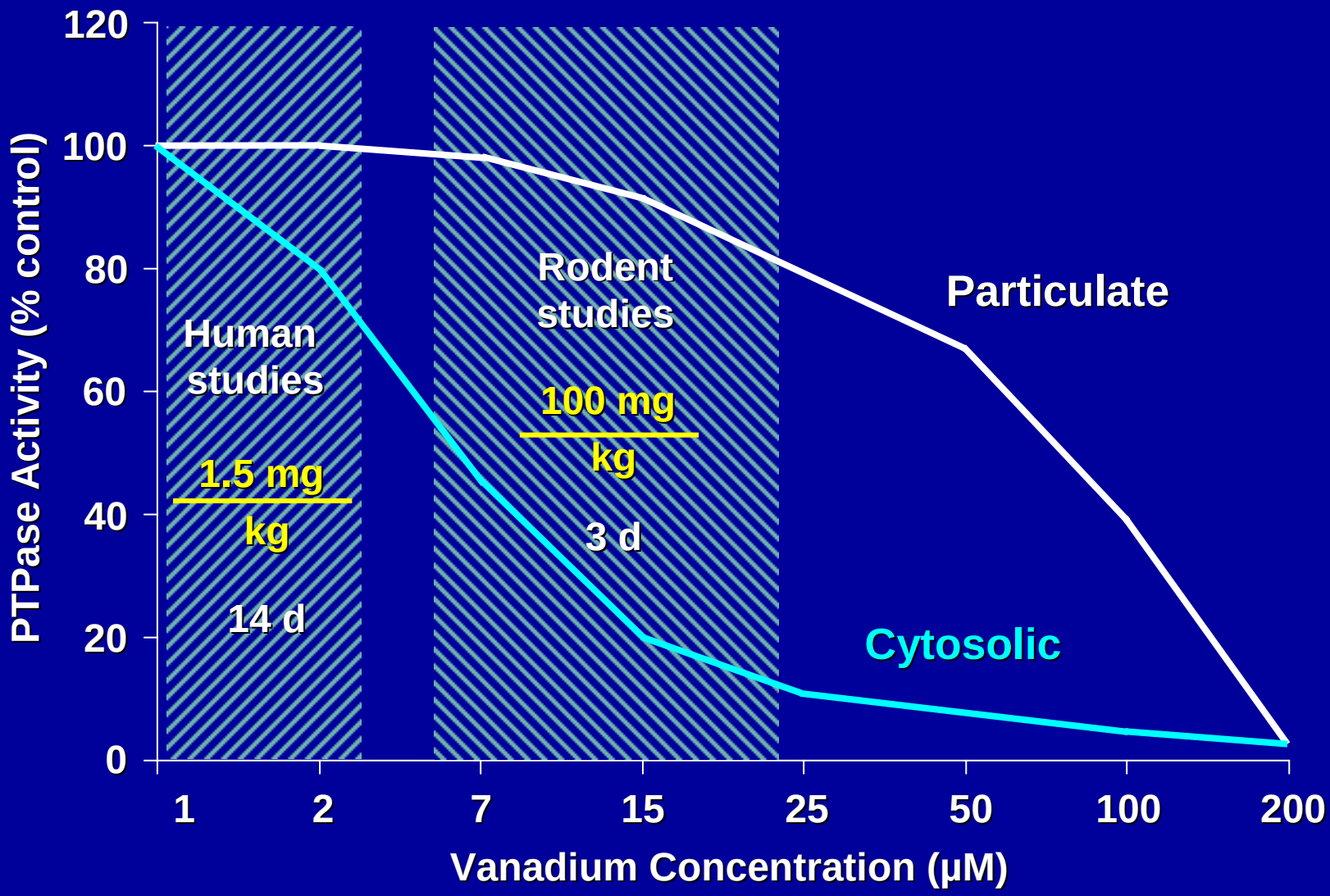


Goldfine et al, Metabolism 49: 400, 2000

Serum Vanadium Concentrations



Serum Vanadium Concentrations



V Supplementation and Human Diabetes: Summary

Generally ineffective in IDDM

Improve insulin sensitivity

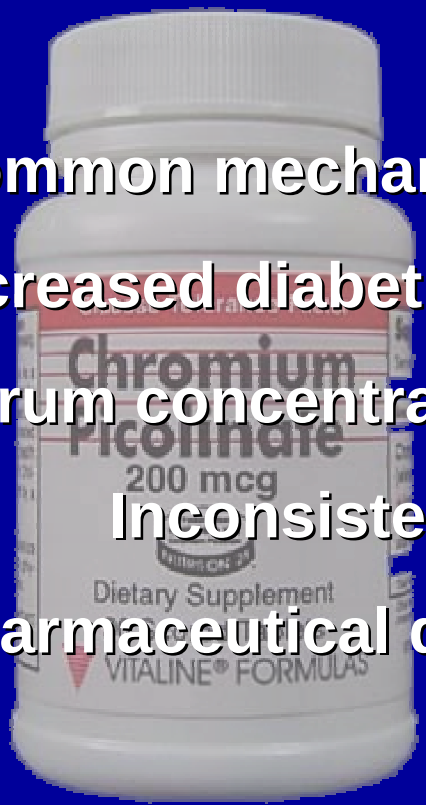
- ↑ glucose use - non oxidative disposal

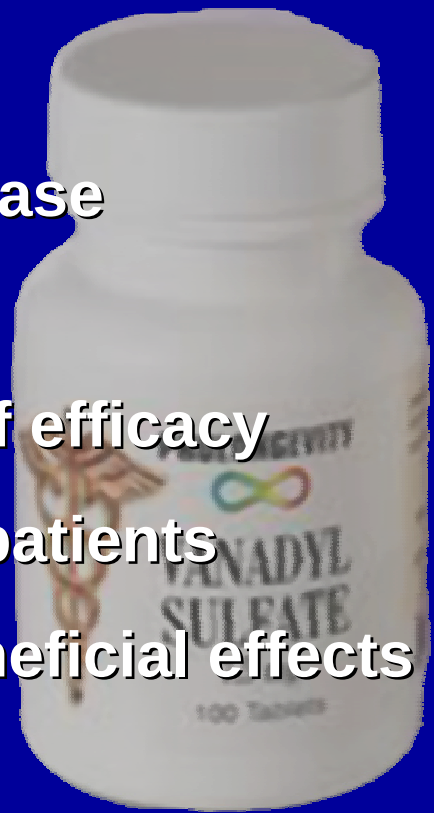
Improve diabetic control

- ↓ HbA1C (50 & 100 mg/d): 7.8 to 6.8 %
- ↓ fasting glucose (100 mg/d): 167 to 144 mg/dL
- ↓ total cholesterol (100 mg/d): 204 to 165 mg/dL
- ↓ 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