

Presentation Objectives

- Diabetes statistics
- What is chromium?
- What is biotin?
- What is Diachrome[®]?
- Discuss the role of chromium (Cr^{+3}) and biotin in insulin and carbohydrate metabolism.
- Discuss the results of Diachrome[®] T2DM clinical trials.
- Economic considerations of Chromium

CDC's Forecast for Diabetes Is Grim

*One in 3 Americans Born
In 2000 Will Get Disease;
Diet, Exercise Show Benefits*

By MARILYN CHASE

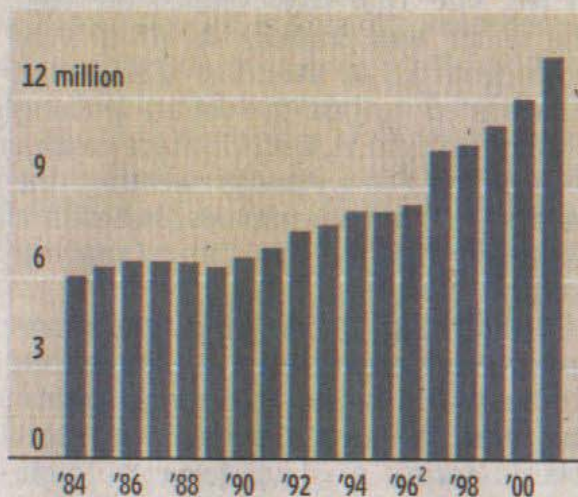
NEW ORLEANS—The U.S. Centers for Disease Control and Prevention predicted that one in three Americans born in 2000 will develop diabetes during his or her lifetime—a forecast that envisions 29 million Americans will be diagnosed, and a further 10 million undiagnosed cases will develop, by 2050.

The CDC's grim forecast, presented here at the American Diabetes Association meeting, increases the urgency of finding strategies to avoid diabetes complications, or prevent the disease altogether with various combinations of diet, exercise and drugs. A study of youth at risk for Type 1 diabetes failed to prevent the condition with oral insulin treatment, but other studies showed that intensive blood-sugar control and lifestyle change produced striking and durable benefits.

Currently 17 million Americans suffer from the disorder of sugar control—a third of them undiagnosed—in an epidemic that is estimated to cost the country \$132 billion a year. About 90% suffer

Spiking Up

Number of Americans with diagnosed diabetes¹



¹Including those who go undiagnosed, about 17 million people have the disease.

²The large increase between 1996 and 1997 is likely due to changes in survey methods.

Source: Centers for Disease Control and Prevention

ing cut the risk of developing Type 2 diabetes by 58%, while metformin cut it by 31%. In the new analysis, the most potent benefit—weight loss—also was toughest to maintain, Dr. Nathan said. After losing an average of 7% of their bodyweight—about 15 pounds for a 200-pound person—participants had gained some of it back four years after the end of the program.

their blood-sugar levels. The follow-up data showed that patients who tested blood sugar and took insulin an average of four times a day continued to have far fewer markers of damage, kidney problems and heart disease than those who were part of the conventional once-daily testing and treatment. This was the case even though people in the conventional treatment group were urged to convert to the tight-control strategy later on, and some of those in the tight-control group were less vigilant after the study ended. This lends support to a theory that hyperglycemia begins early on to produce stubborn byproducts that burrow into blood-vessel walls, muscles, eyes or kidneys, causing a range of chronic organ damage.

"I call it metabolic memory," said Harvard's Dr. Nathan of this surprise finding in this follow-up, called the Epidemiology of Diabetes Interventions and Complications study. People who treat early and hard may benefit for years, even if treatment discipline lapses. But for those who shun sugar-control early, assuming that heart, eye or kidney complications won't happen for 10 to 15 years, he said, "the cards may have already been dealt."

Meantime, hopes for an effective new strategy to prevent Type 1 diabetes were dashed. Researchers gave either oral insulin or a placebo to 372 people aged 12 to 25 with Type 1 diabetes. The study

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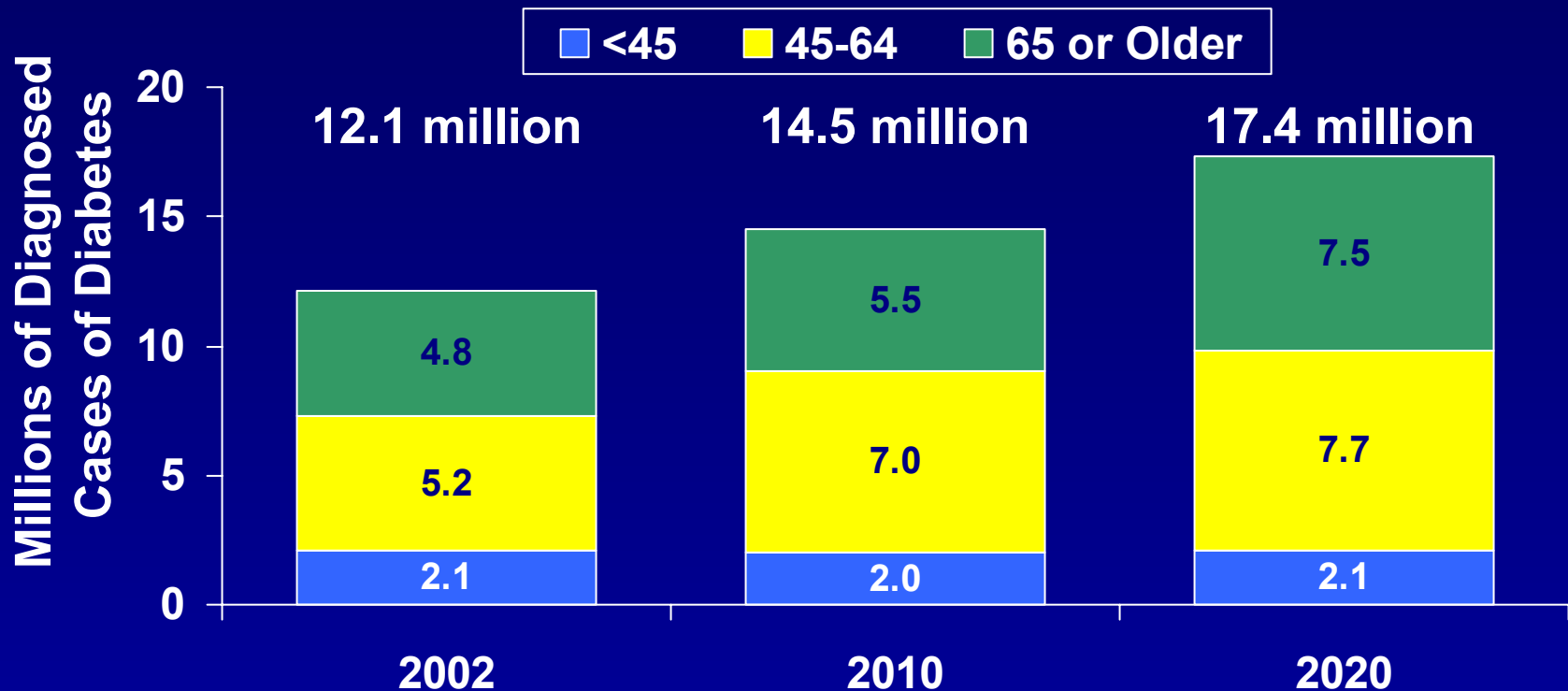
USA TODAY 2002

WEAPONS
OF MASS
EXPANSION.



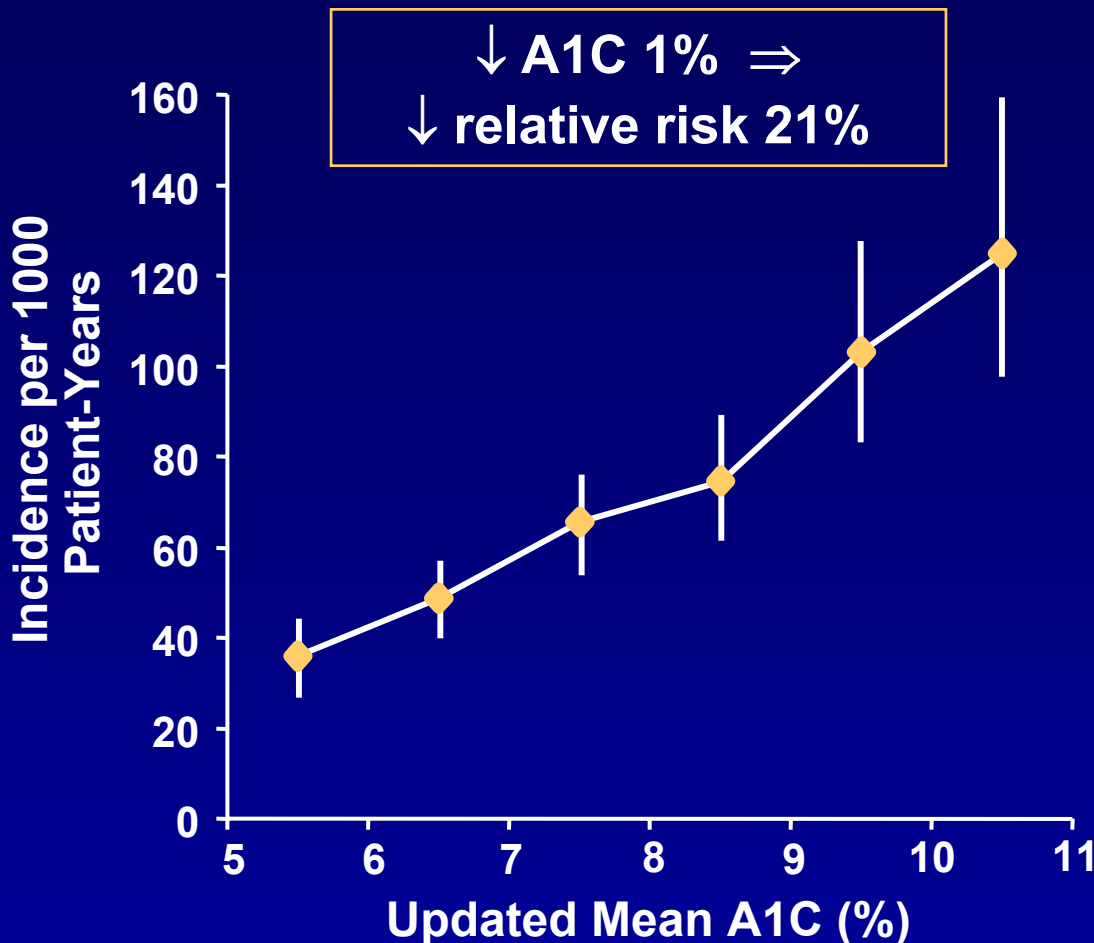
Cases of Diagnosed Diabetes in the U.S. by Age

**Cases of *diagnosed* diabetes are projected to increase
by 44% by 2020**



Relationship Between Glycemia and Complications

Any endpoint related to diabetes



Any endpoint related to diabetes included fatal and nonfatal macrovascular and microvascular events

Aggressive Control of Type 2 Diabetes is Critical

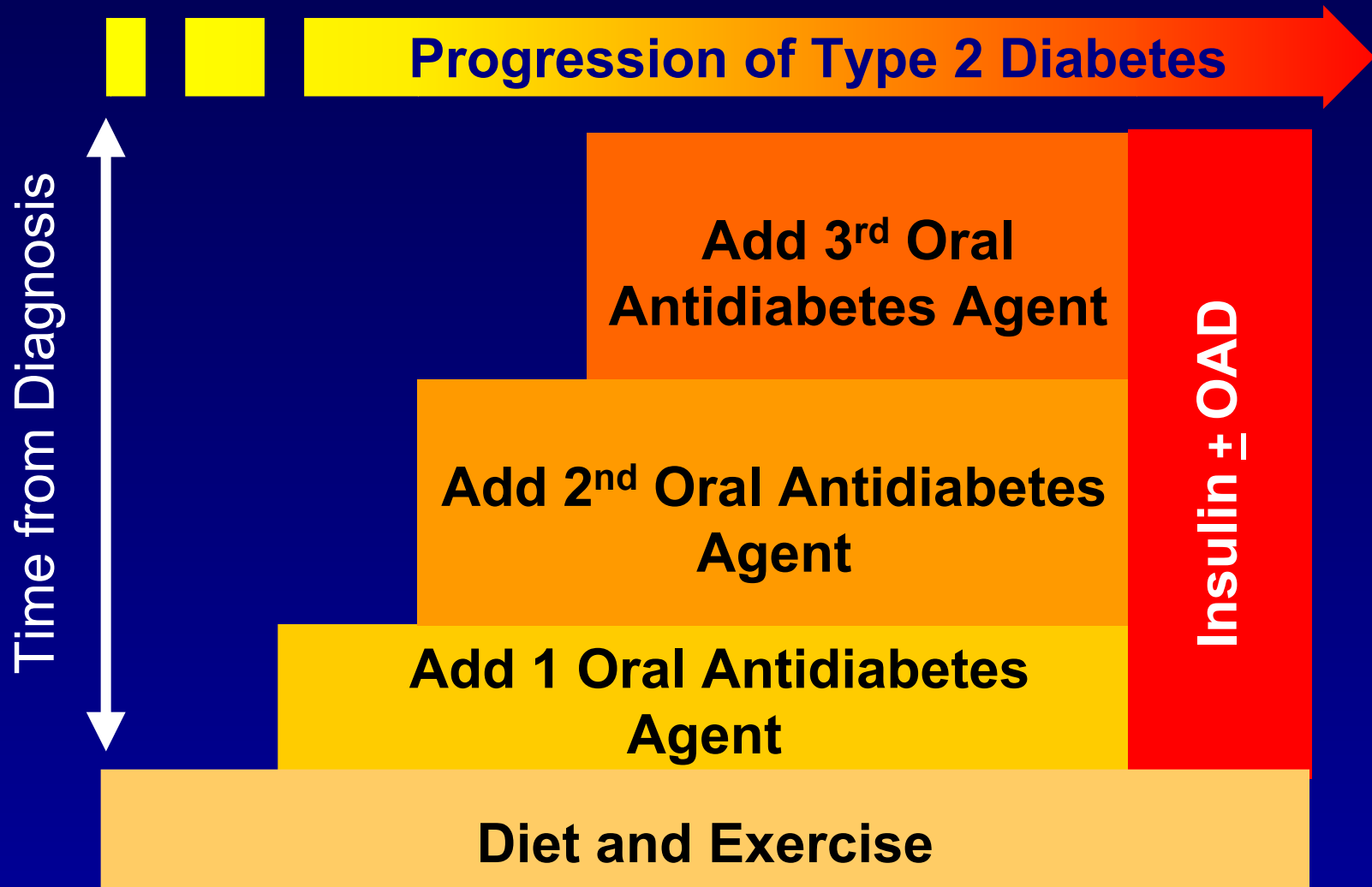
American Diabetes Association

	<u>Normal</u>	<u>Goal</u>
A1C (%)	<6	<7
Preprandial plasma glucose (mg/dL)	<110	90-130

American Association of Clinical Endocrinologists

A1C (%)	<6	≤6.5
Preprandial plasma glucose (mg/dL)	<110	<110

Traditional Treatment Approach Adds Medications Sequentially



Nutritional Goals

- Individualized meal planning
- Balance food intake with medications and exercise
- Maintain reasonable weight

What about Chromium?

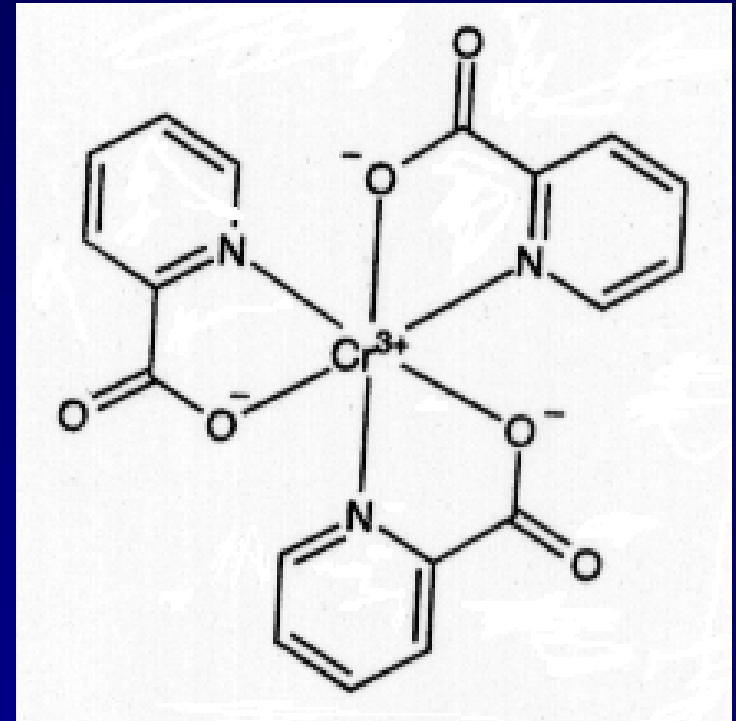
- Chromium is an essential cofactor for the hormone insulin which regulates the metabolism of protein, fat and carbohydrates.
- Chromium is a trace element found in brewers yeast, broccoli, organ meats, whole grains, cheese and nuts.

Chromium and Diet

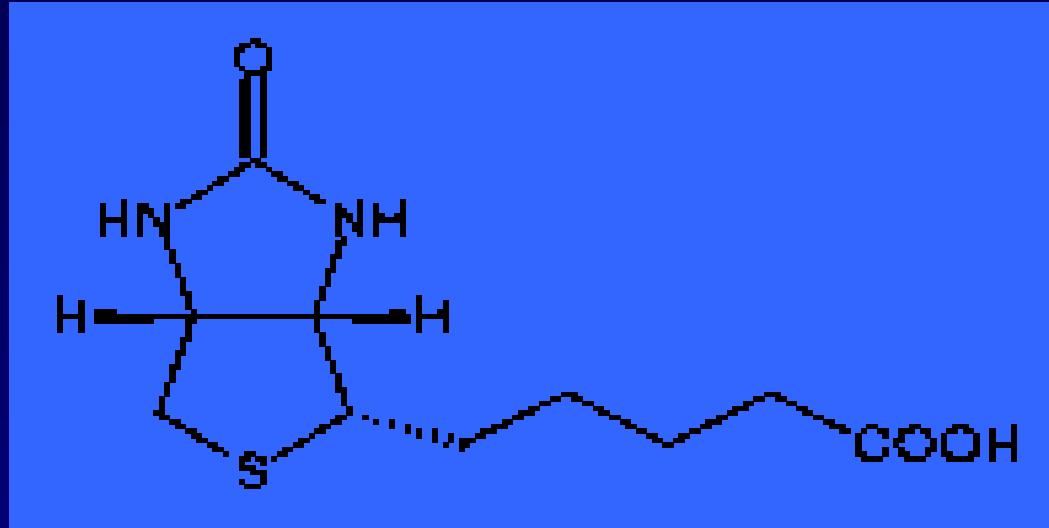
- Inadequate amount of chromium in the US diets
 - foods containing chromium not frequently eaten
 - chromium is lost during food processing
- Diets rich in sugar and carbohydrates cause a loss of chromium
- lower Cr levels than normal in obese and/or diabetes
- Chromium levels with age

What is Chromium Picolinate?

- Complex of chromium (Cr^{3+}) and picolinic acid
- Cr is an essential trace mineral
- Picolinic acid is a natural metabolite of tryptophan
 - Found in higher levels in human breast milk
- Picolinic acid enhances the absorption/bioavailability of Cr



What is biotin?



Biotin; a water soluble B vitamin

(C₁₀H₁₆N₂O₃S) ; MW = 224.31

- Stimulates activity of glucokinase
- Improves pancreatic β -islet cell function
- Regulates conversion of glucose to FA

CrPic Clinical Studies: Diabetes

Investigator	Form of Diabetes	# Pts.	Daily Dose of Chromium (picolinate)	Concomitant Antidiabetic Medication	Study Duration	Publication	Study Results
Kleefstra, 2006	Type 2	52	500 mcg 1000mcg	antidiabetic meds. Insulin >50U	6 mos.	Diab. Care	No change
Ghosh, 2002	Type 2	50	200 mcg	antidiabetic meds.	3 mos.	J Nutr Biochem	↓ HbA1c(p<0.05), ↓ fasting & pp glucose (p<0.001)
Morris, 2000	Type 2	5	400 mcg	none (diet alone)	3 mos.	Diab. Med.	↓ insulin resistance (p<0.01)
Rabinovitz, 2000	Type 2	39	400 mcg	antidiabetic meds.	3 weeks	Gerontol.	↓ fasting glucose
Cheng, 1999	Type 2	833	500 mcg	hypoglycemic meds.	9 mos.	JTEEM	↓ fasting glucose (p<0.05)
Bahadori, 1999	Type 2	16	1000 mcg	sulphonylurea and metformin	4 mos.	Diabetes	↓ fasting insulin (p<0.05)
Ravina, 1999	Steroid-Induced	44	600-300 mcg	glibenclamide, metformin, insulin	1-2 weeks	Diab. Med.	38/41 pts. ↓diabetic symptoms, ↓ 50% meds.
Jovanovic, 1999	Gestational	20	4-8 mcg/kg (300-800 mcg)	insulin or none	2 mos.	JTEEM	↓ glucose & insulin levels (p<0.05)
Cefalu, 1999	Obese-Pre Diabetic	29	1000 mcg	none	8 mos.	JTEEM	↑ insulin sensitivity (p<0.005)
Anderson, 1997	Type 2	180	1000 mcg	glibenclamide or glipizide	4 mos.	Diabetes	↓ HbA1c, fasting glucose & insulin (p<0.05)
Ravina, 1995	Type 1&2	162	200 mcg	sulphonylurea, metformin or insulin	3 mos.	JTEEM	↑ insulin sensitivity (p<0.001)
Lee, 1994	Type 2	30	200 mcg	insulin, oral meds, or diet	2mos.	Diab. Care	No difference in glucose control
Evans, 1989	Type 2	11	200 mcg	hypoglycemic meds.	1.5 mos.	Int J Bio Med	↓ HbA1c, (p<0.05)

Chromium Picolinate Safety

- Genotoxicity Studies (5)
- Sub-chronic (90 day) Mice/Rats (NTP)
- Sub-chronic (20 wk) Rat Toxicity (Anderson, 1997)
- Human Genotoxicity Study (Kato, 1998)
- 5 Isolated Case Reports - Never Duplicated
- No adverse effects seen in 30+ clinical studies
- Generally Recognized As Safe affirmed (2000)
- Institute of Medicine 2004 Review Supports Safety
- UK FSA (2004): CrPic Safe For Use Up To 10 mg/d
- FDA QHC (2005): Finds CrPic Safe For Intended Use

Biotin - Safety

- No toxic effects reported
- No AEs with 200 mg orally
- No LOAEL (Lowest Observed Adverse Event Level)
- NOAEL = 2500 mcg (2.5 mg)
- GRAS (Generally Recognized as Safe)

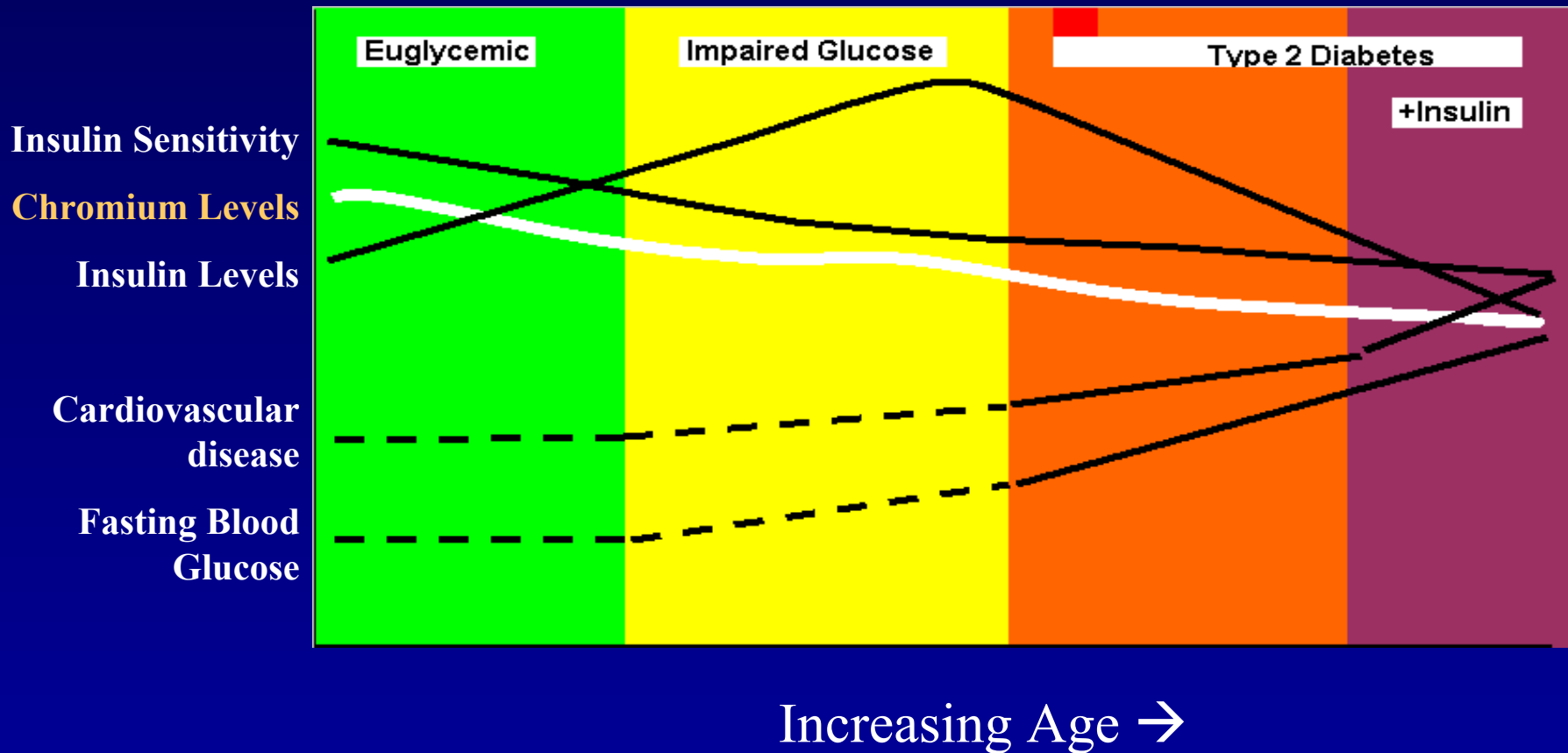
What is Diachrome®?

- An adjuvant comprised of:
 - Chromium Picolinate (600 mcg Cr^{+3})
 - Biotin (2 mg)
- Dual benefits include reduction of elevated blood glucose and improvement in blood lipids
- Once a day administration

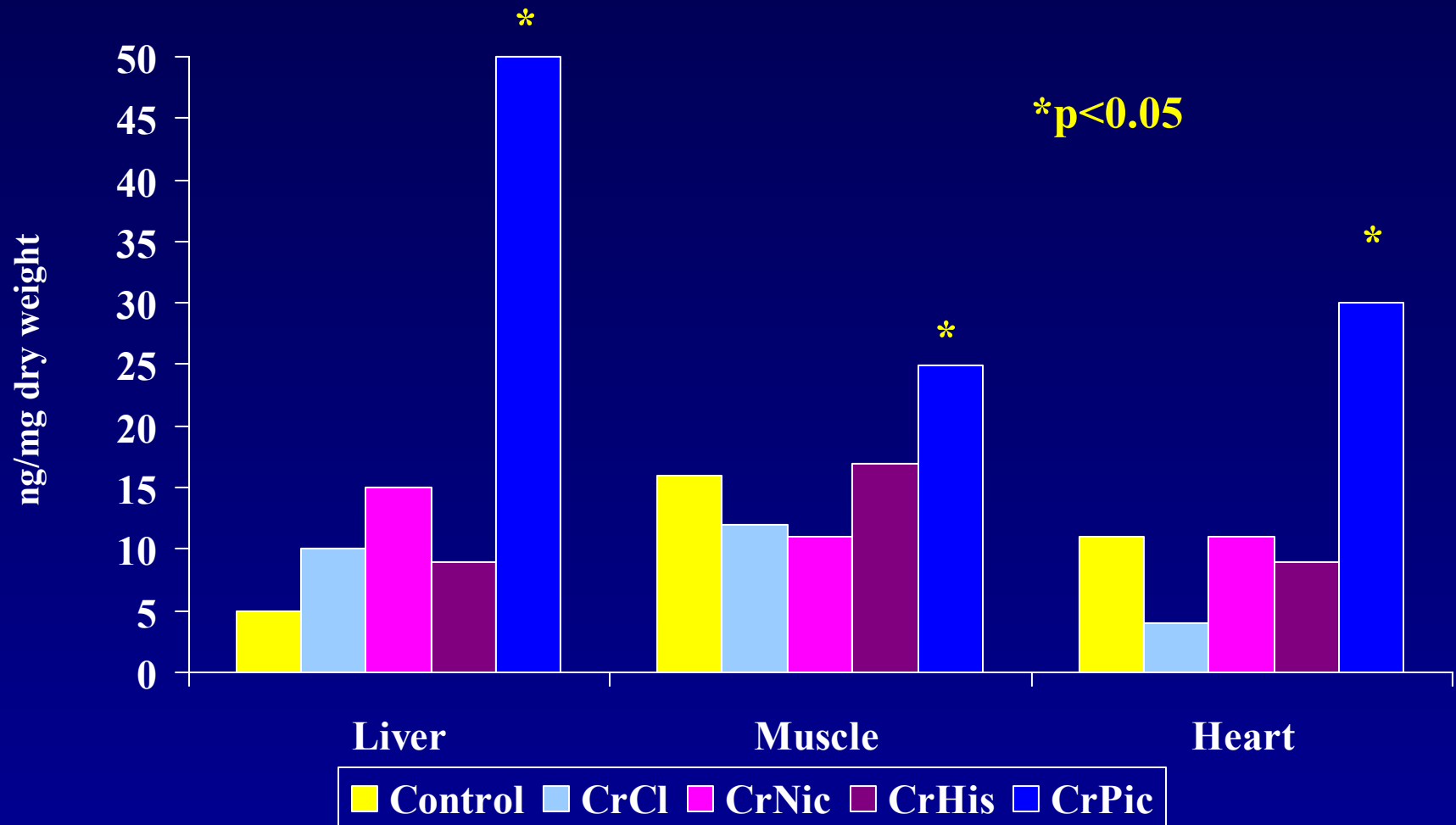
- Diachrome is currently available at CVS and Duane Reade pharmacies
- Suggested Retail Price of \$24.99 for a 60-day supply



Cr Levels Over Time (Progression of Diabetes)



Chromium in Tissues

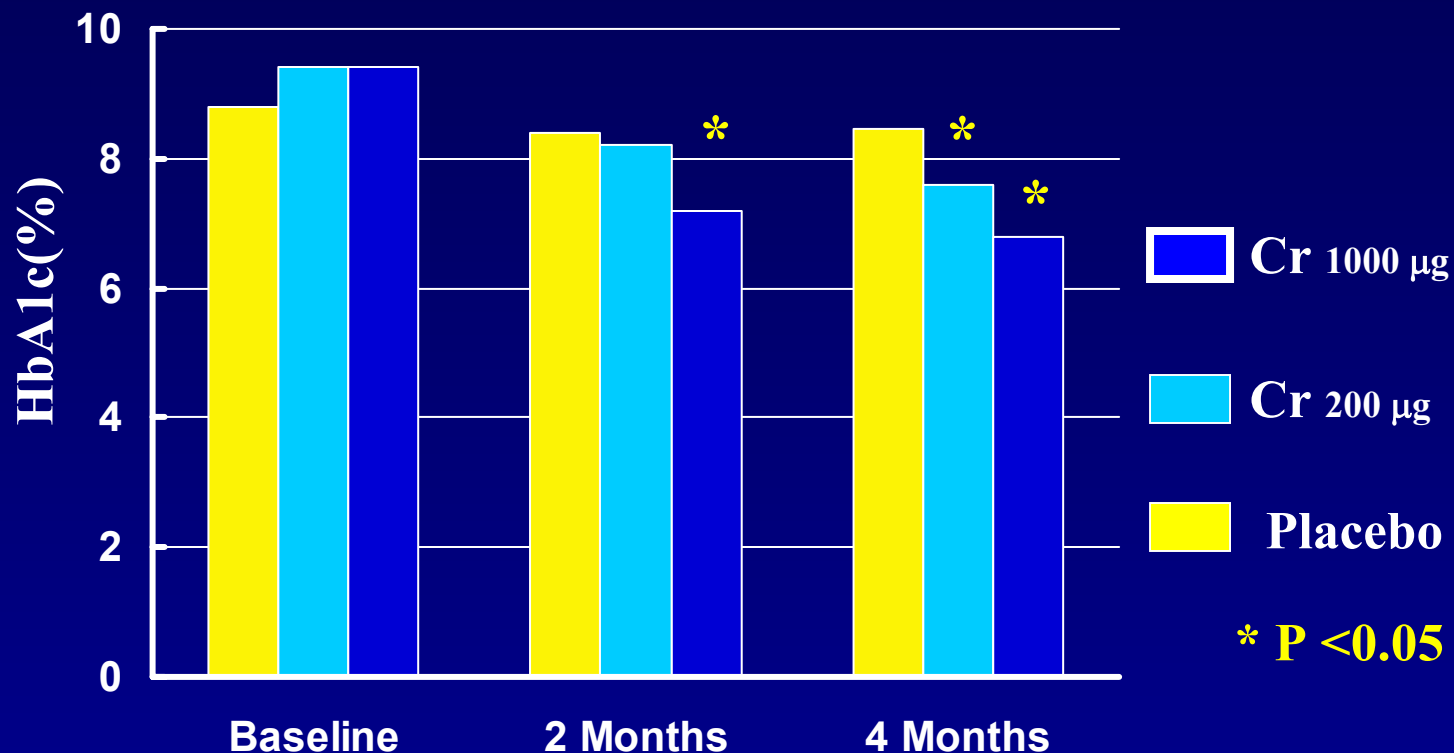


Source: Anderson et al., *The Journal of Trace Elem. In Experimental Medicine* (9): 11-25, 1996

Clinical Studies in Subjects with Diabetes (Effect on Blood Glucose Control)

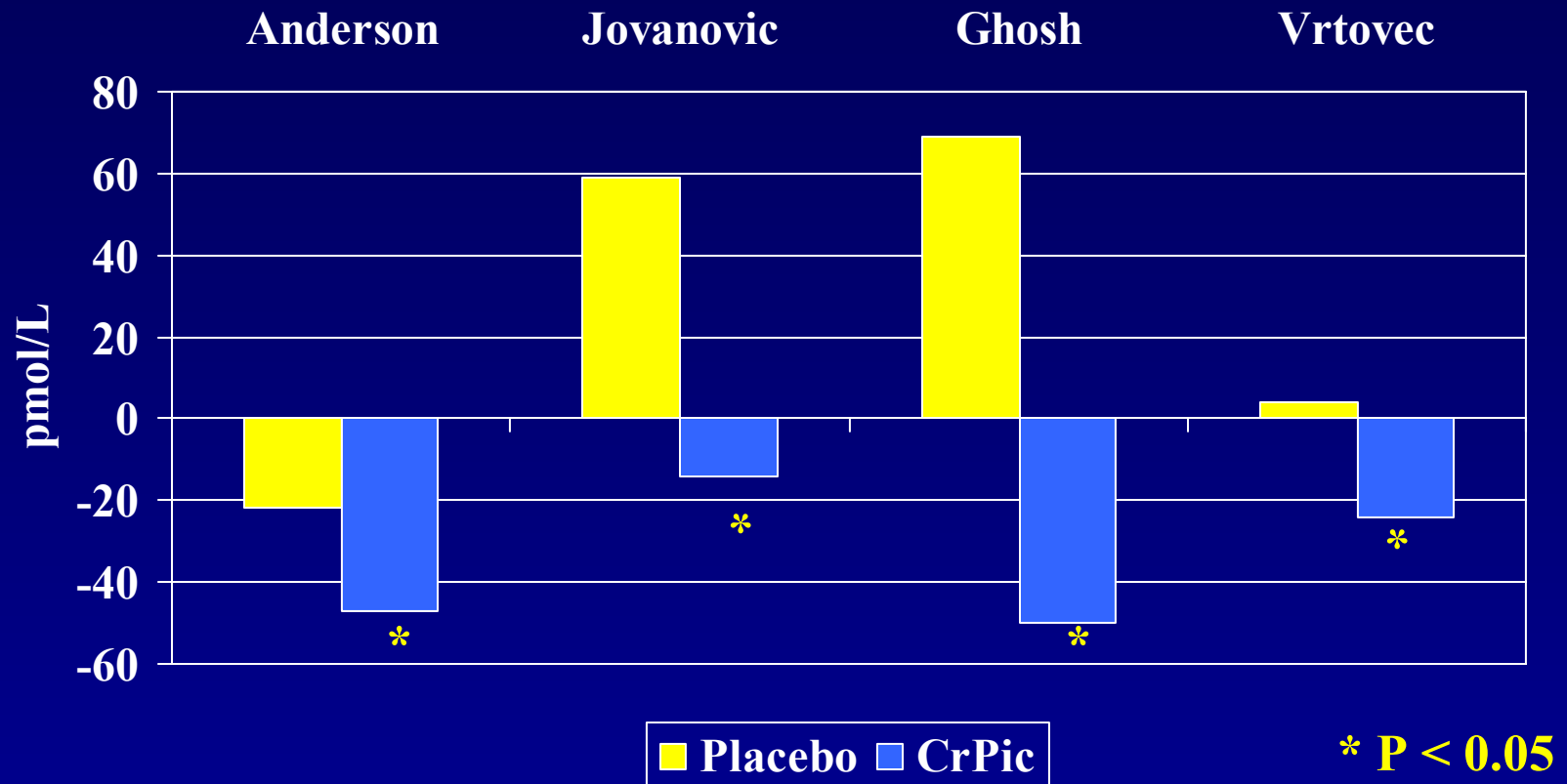
	Significant Benefit
All Studies Using Cr	16/32 (50%)
Studies w. CrCl_3	2/12 (17%)
Studies w. Cr-other	2/6 (33%)
Studies w. CrPic	12/14 (86%)

Clinical Evidence Shows Chromium Picolinate Reduces Elevated Glycated Hemoglobin Levels

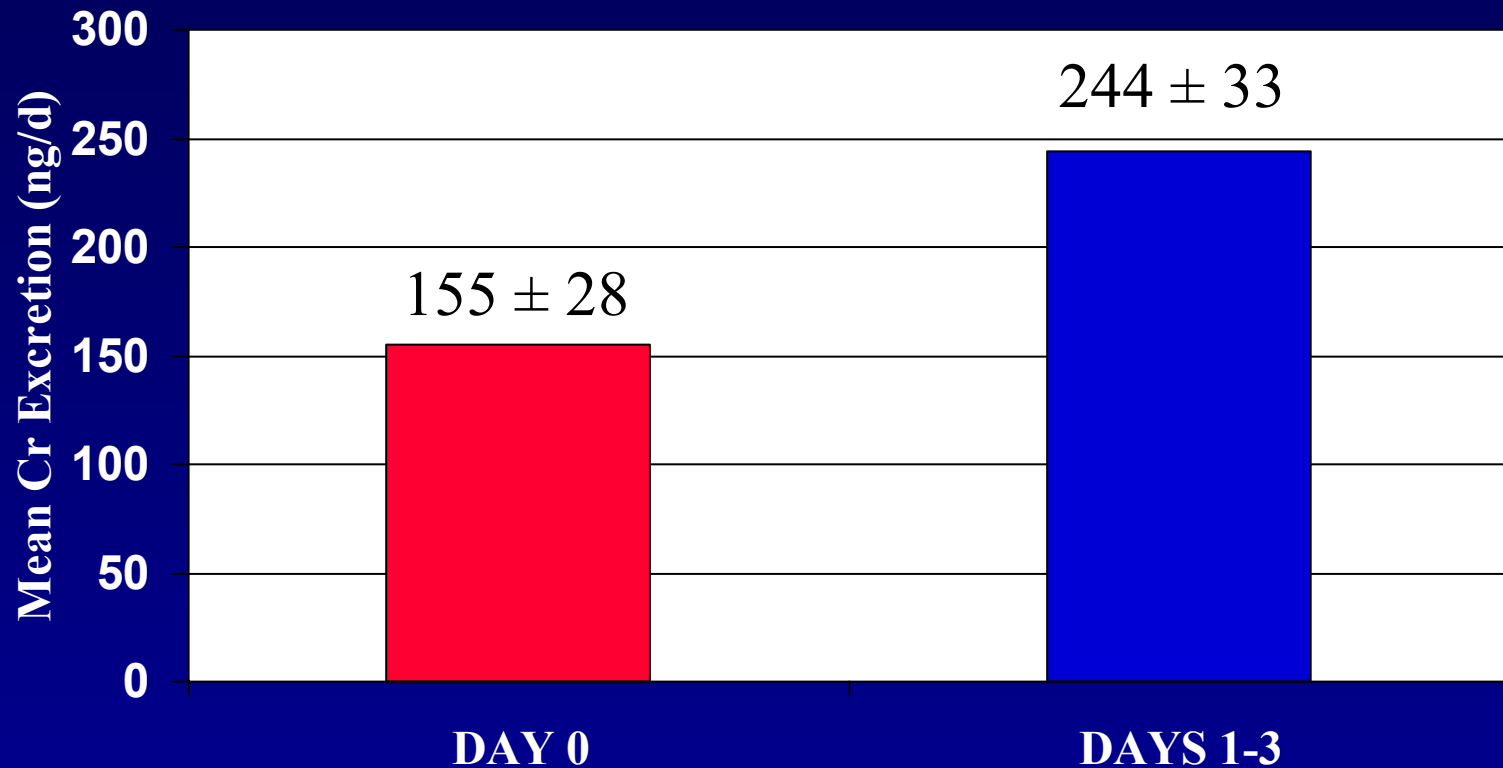


Anderson et al. Elevated Intakes of Supplemental Chromium Improve Glucose and Insulin Variables in Individuals With Type 2 Diabetes, Diabetes 1997 ;46:1786-1791

Change in Fasting Insulin with CrPic



Mean Urinary Chromium Losses Following Corticosteroid Treatment (n=13)



CrPic Treatment of Steroid-Induced Diabetes

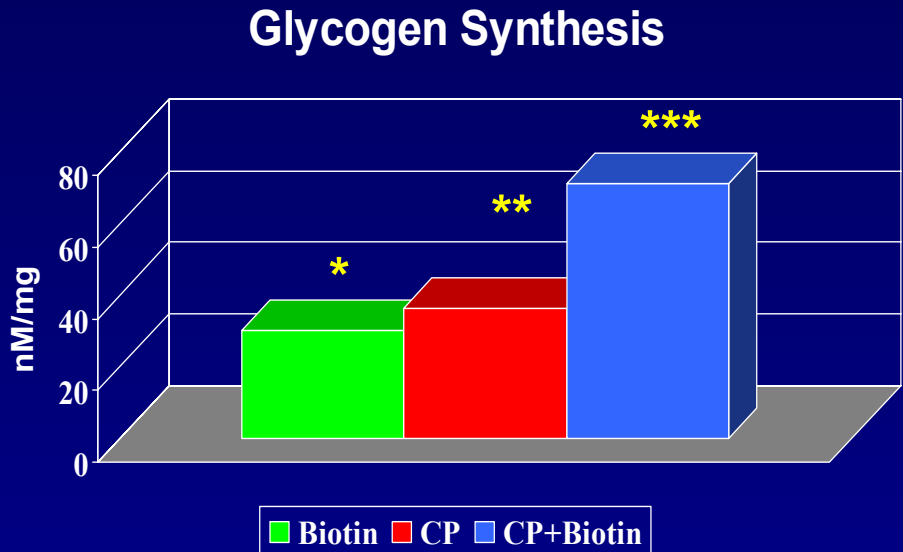
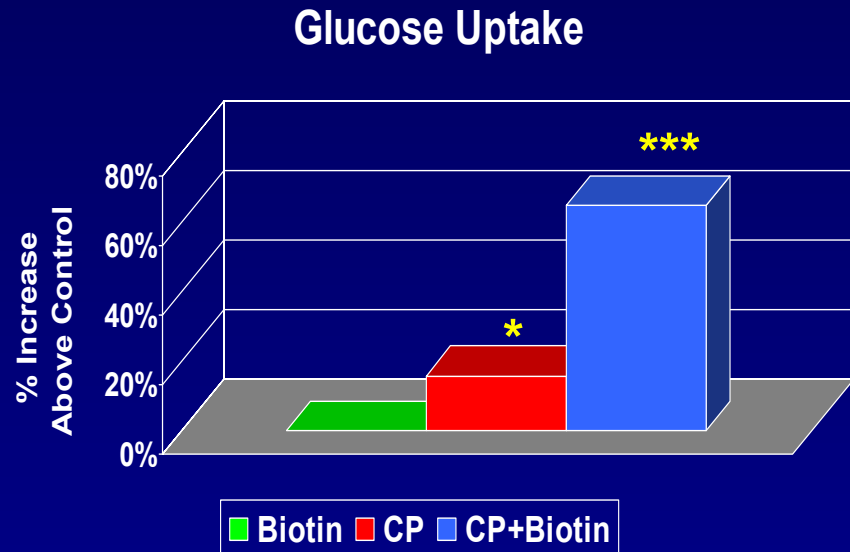
- 49 of 52 pts. reacted satisfactorily
- Fasting blood glucose levels decreased from 250 mg/dl to 150 mg/dl
- 5 pts. stopped taking hypoglycemic agents (sulfonylureas or insulin injections) and did well on Cr supplementation alone.

Diachrome[®] Studies

- In Vitro
 - Human Skeletal Muscle Cells
- Preclinical
 - JCR La:cp Rat Model
- Clinical
 - PEP (Open Label Program) N=40
 - Beverage (DBPC Study) N=34
 - Glycemic Index (DBPC Study) N=43
 - T2DM 90 day (DBPC Study) N=447
 - T2DM 270 Day Extension N=28

CP+Biotin: Skeletal Muscle Cell Culture

(Glucose Uptake & Glycogen Production)

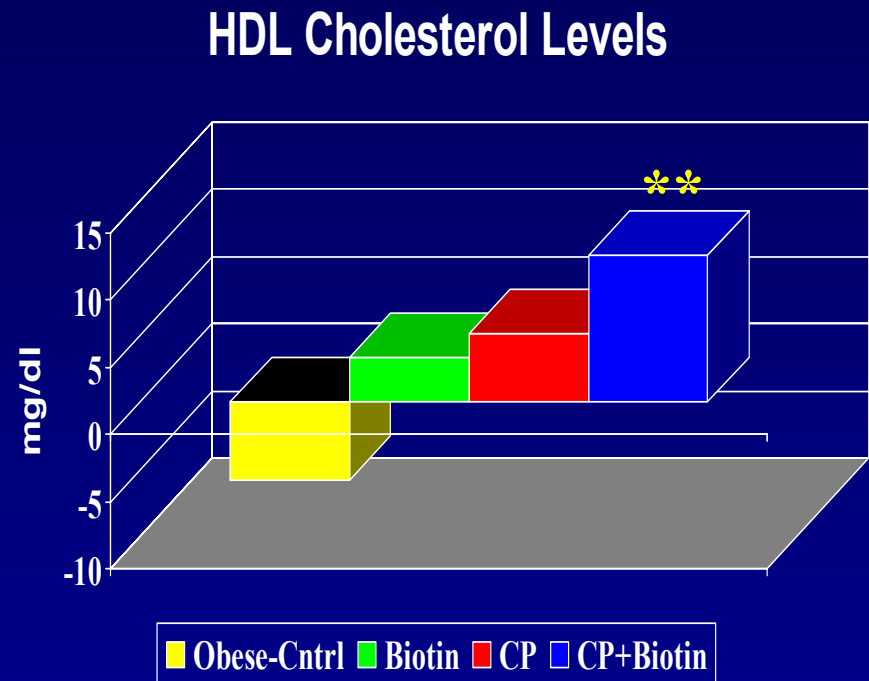
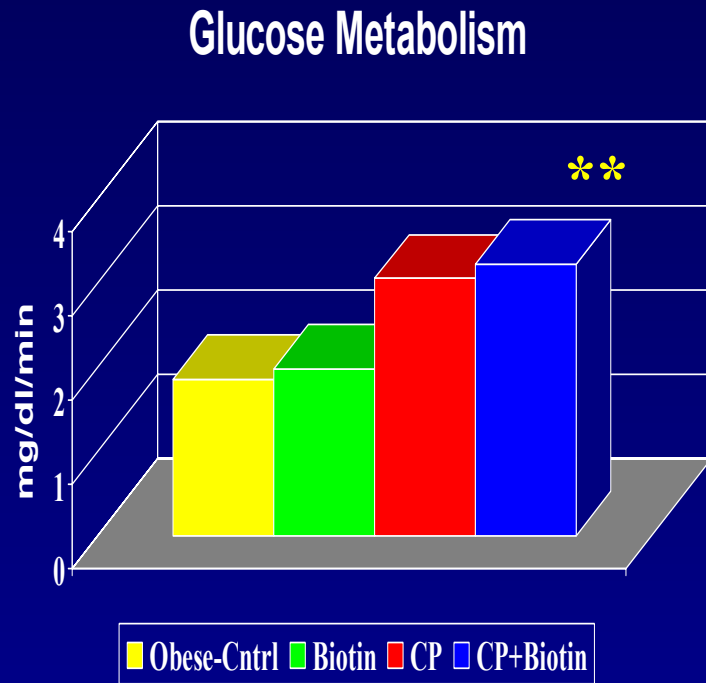


* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Wang et al, 2000 17th Annual IDF Congress

Animal Study (JCR Rats)

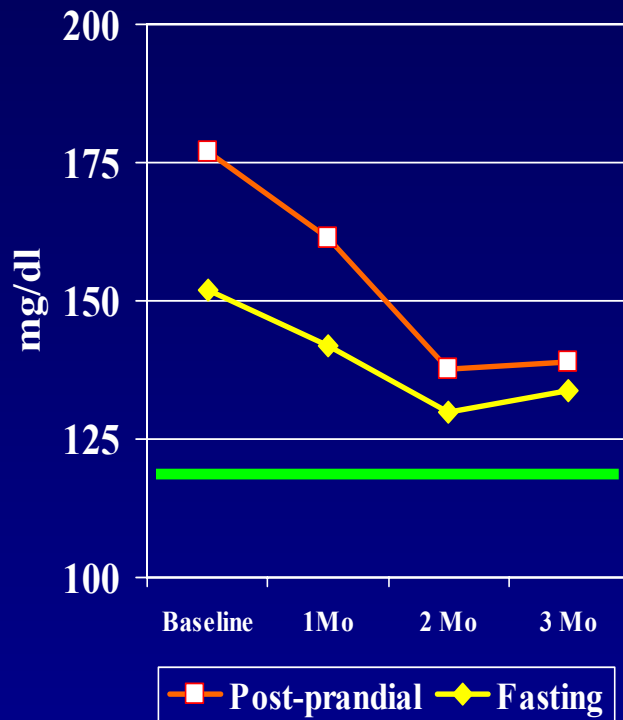
Glucose Metabolism & HDL Cholesterol



**** P < 0.01**

Source: Komorowski, et al., Society for the Study of Ingestive behavior. Abs, pp:41, 2001

Diachrome[®] PEP Program *



- Open-label program in patients with type 2 diabetes
- Program showed improvements in blood sugar control

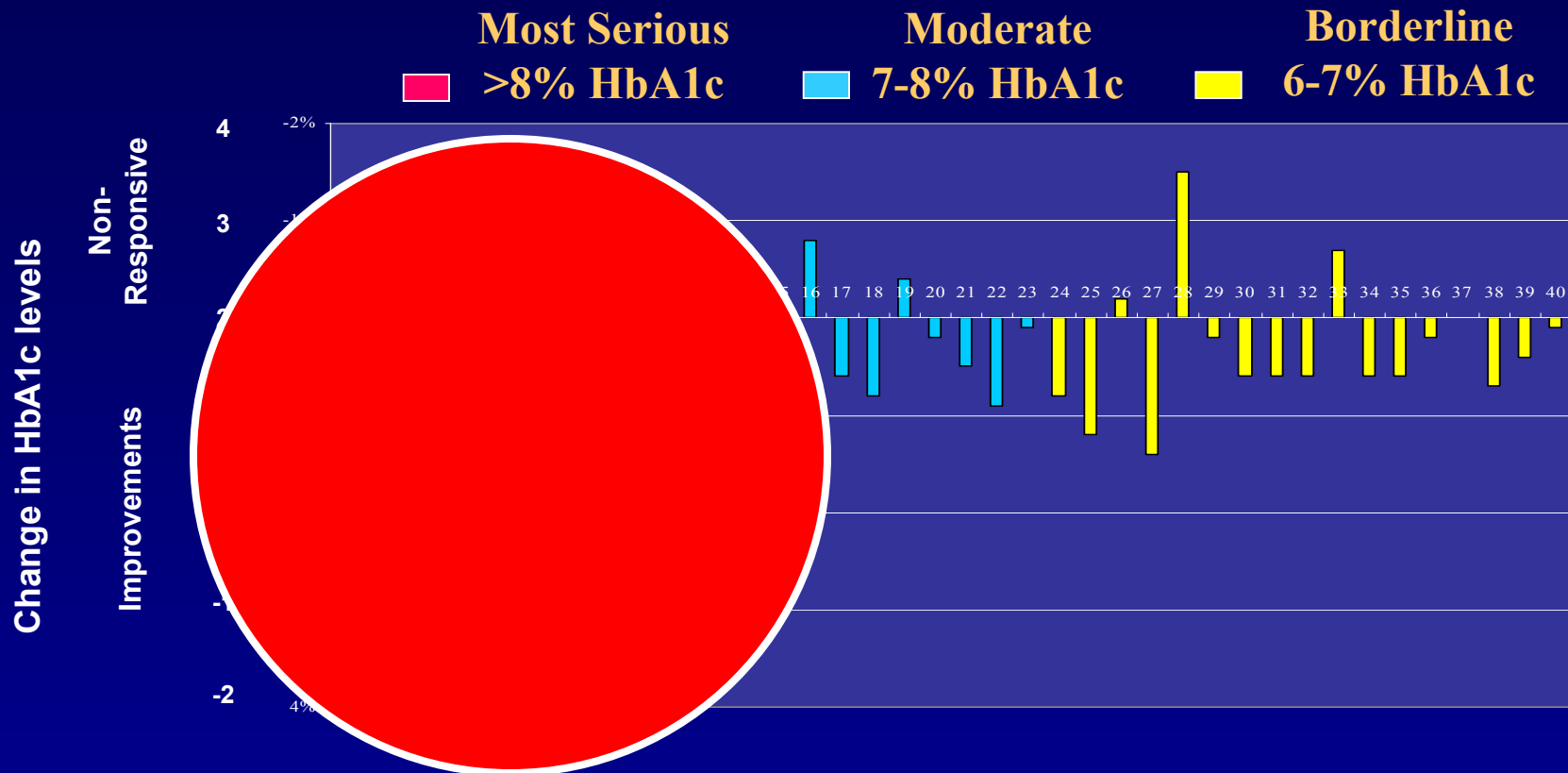
Δ PPG = - 37.8 mg/dL ; P < 0.01

Δ FPG = - 18.3 mg/dL ; P < 0.05

* Juturu, et al. Trace Elements and Electrolytes (23) 1:66-72, 2006

Diachrome[®] : PEP Results

(12 week change in HbA1c levels, 40 subjects)



Initial HbA1c in Decreasing Order (13.6% - 6.0%)

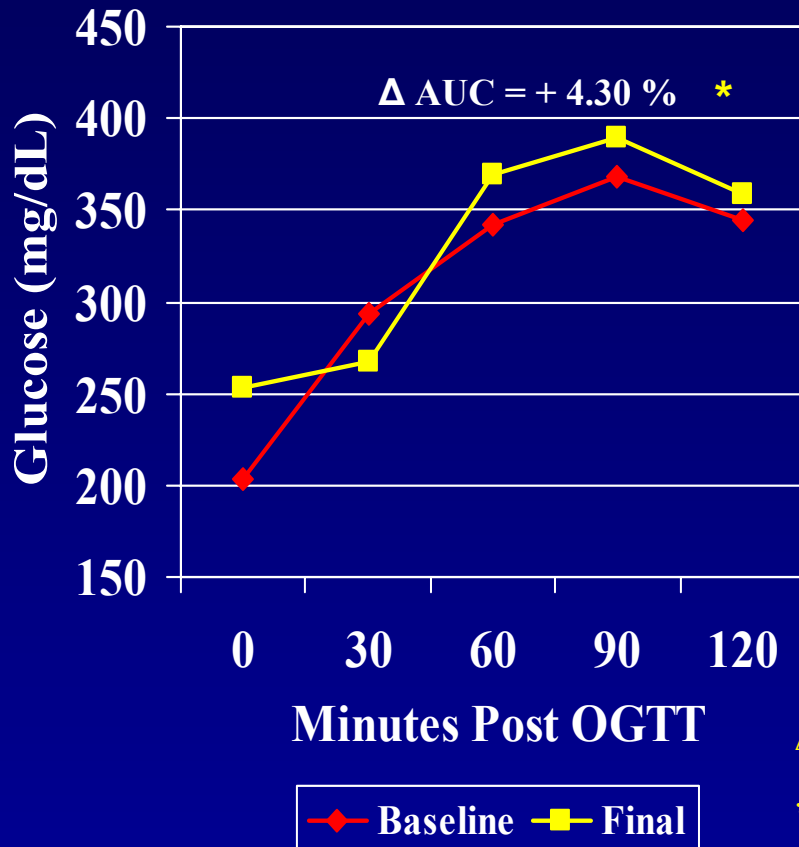
Ex.: Subject 1 – Initial HbA1c 13.6% → with Diachrome, 10.0%

- 87% response rate
- Average 1.7% change in patients over 8%

Diachrome[®] 30-Day Clinical Study

Glycemic Index

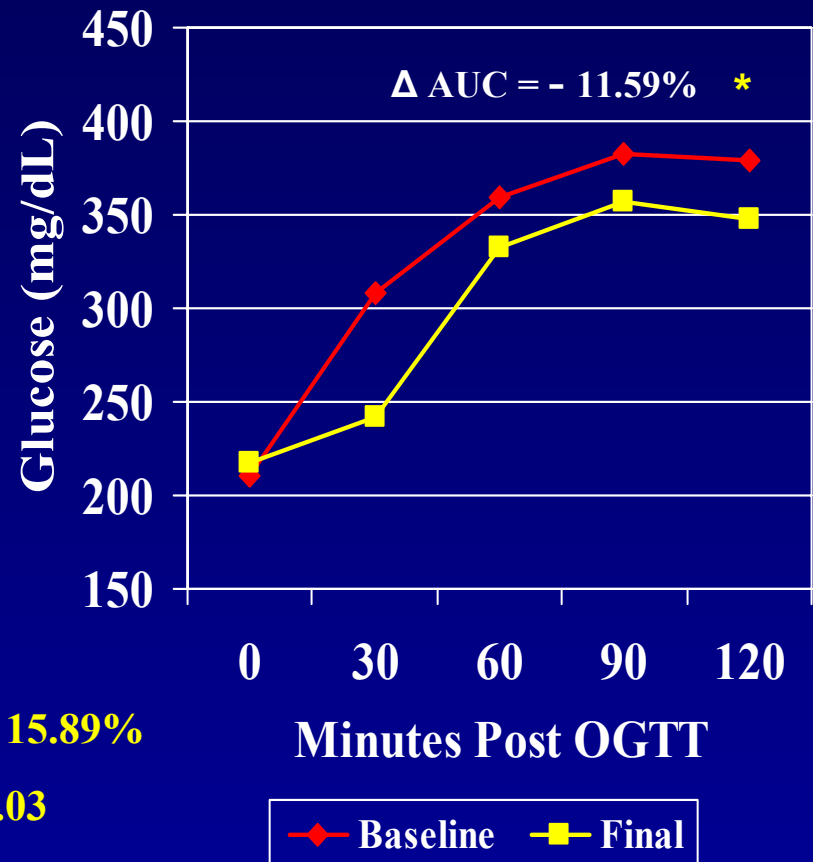
OGTT - Placebo



$\Delta_{AUC} = 15.89\%$

* P < 0.03

OGTT - Diachrome



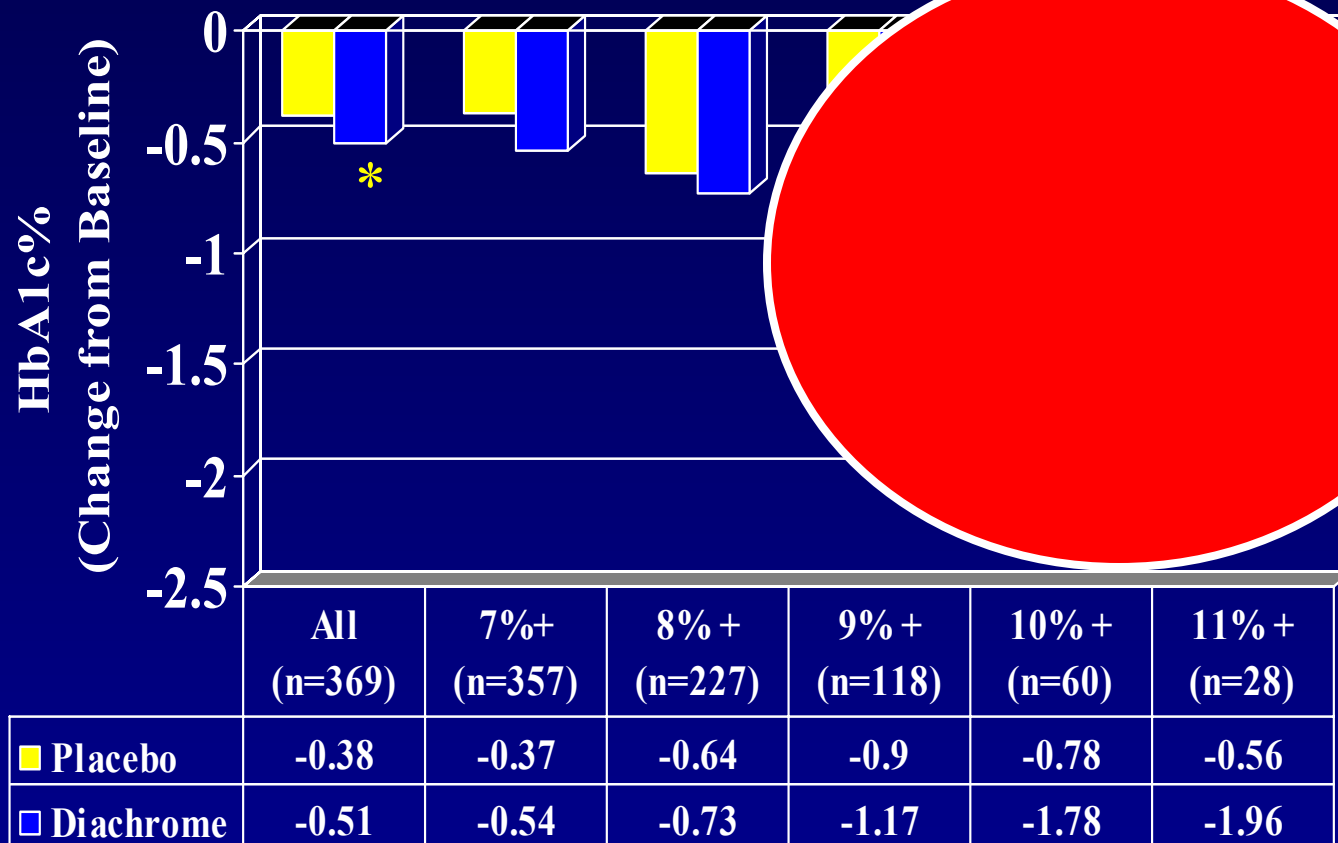
Nutrition 21 CPB-02003

Diachrome[®] 90 Day Type 2 DM

- Randomized, Double Blinded, Placebo Controlled
- Multi-geographical Study Centers; N= 17
- Inclusion Criteria:
 - Male or Female; 18-70
 - BMI ≥ 25 and < 35
 - HbA1c $\geq 7.0\%$
 - Stable OADs > 60 days
- Total Enrolled: 447
 - Cauc. 221; Hisp. 147; Blk. 48; Asian 23; Other 8
 - Male 258; Female 189
- Intent To Treat: 369
 - At least one dose of study med
 - One A1c assessment post Baseline Visit

Diachrome[®] Study Results

Effect on HbA1c Levels



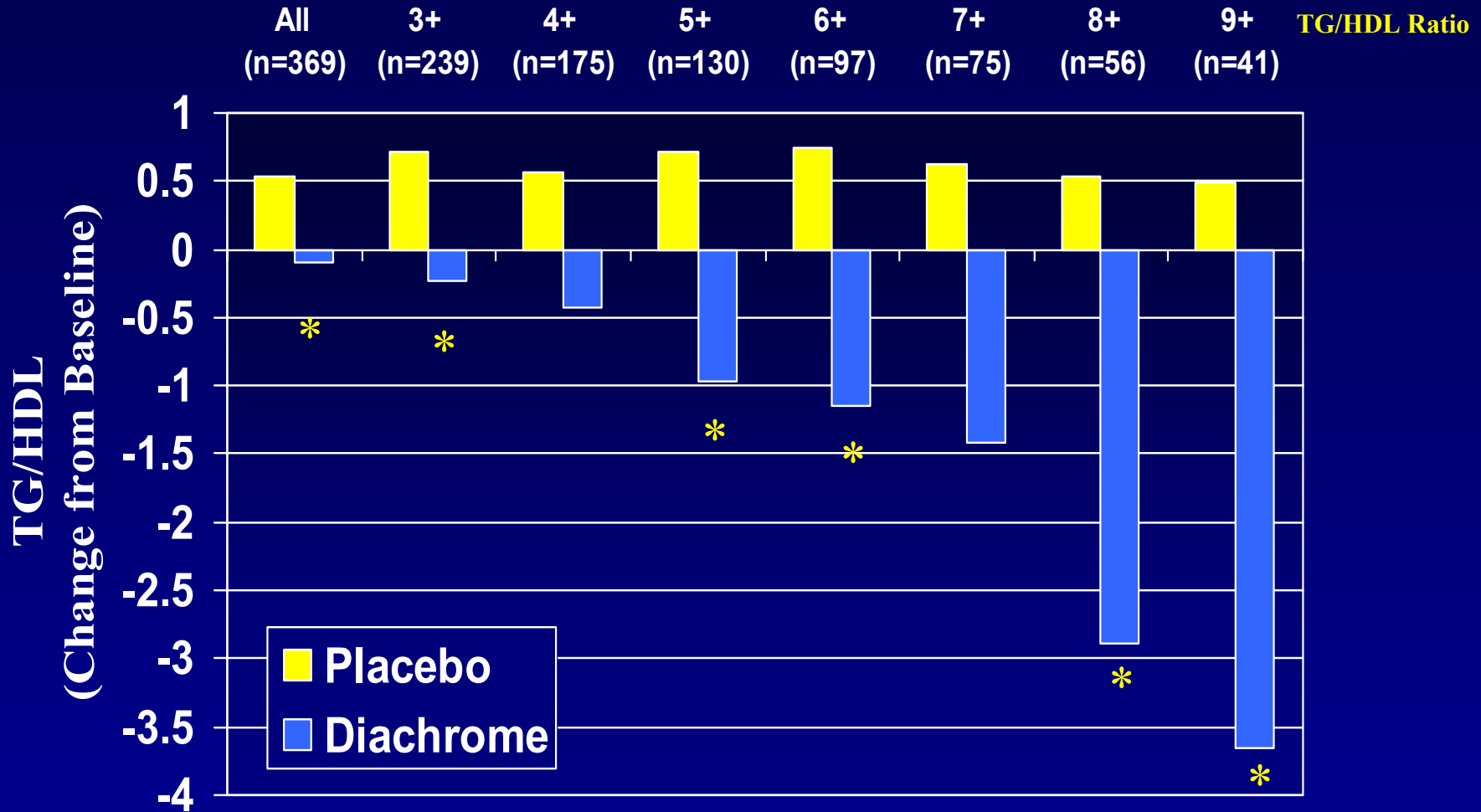
“All” = all subjects with baseline and final visits; “n %+” = subjects with baseline HbA1c levels \geq n %

* $p < 0.008$ for ANCOVA (treatment * baseline HbA1c) compared to placebo

** $p < 0.05$ compared to placebo

Diachrome® Study Results

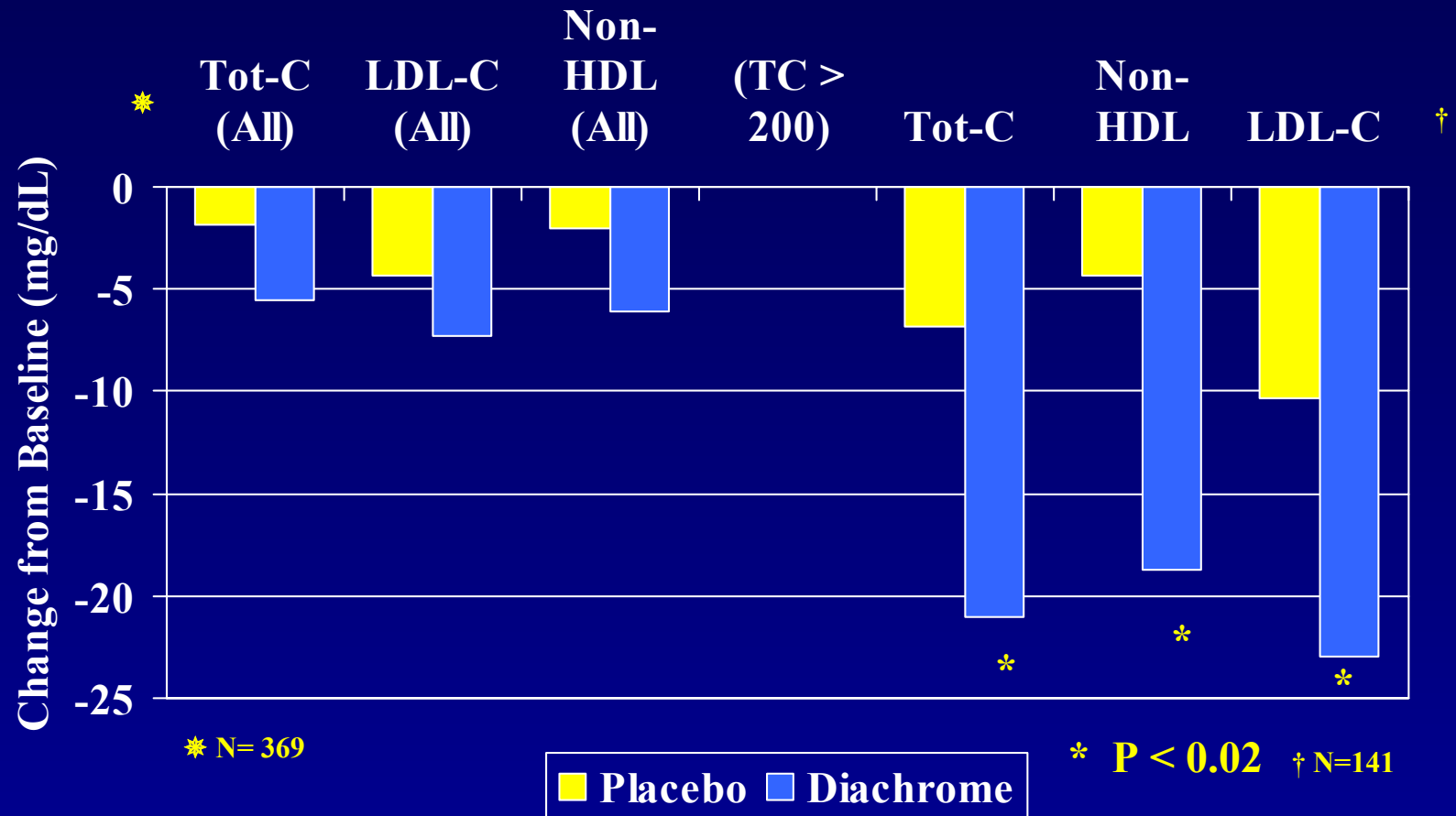
Effect on TG/HDL Ratio



“All” = all subjects with baseline and final visits; “n+” = subjects with baseline TG/HDL \geq “n”
* P < 0.05 active vs. placebo

Diachrome® Study Results

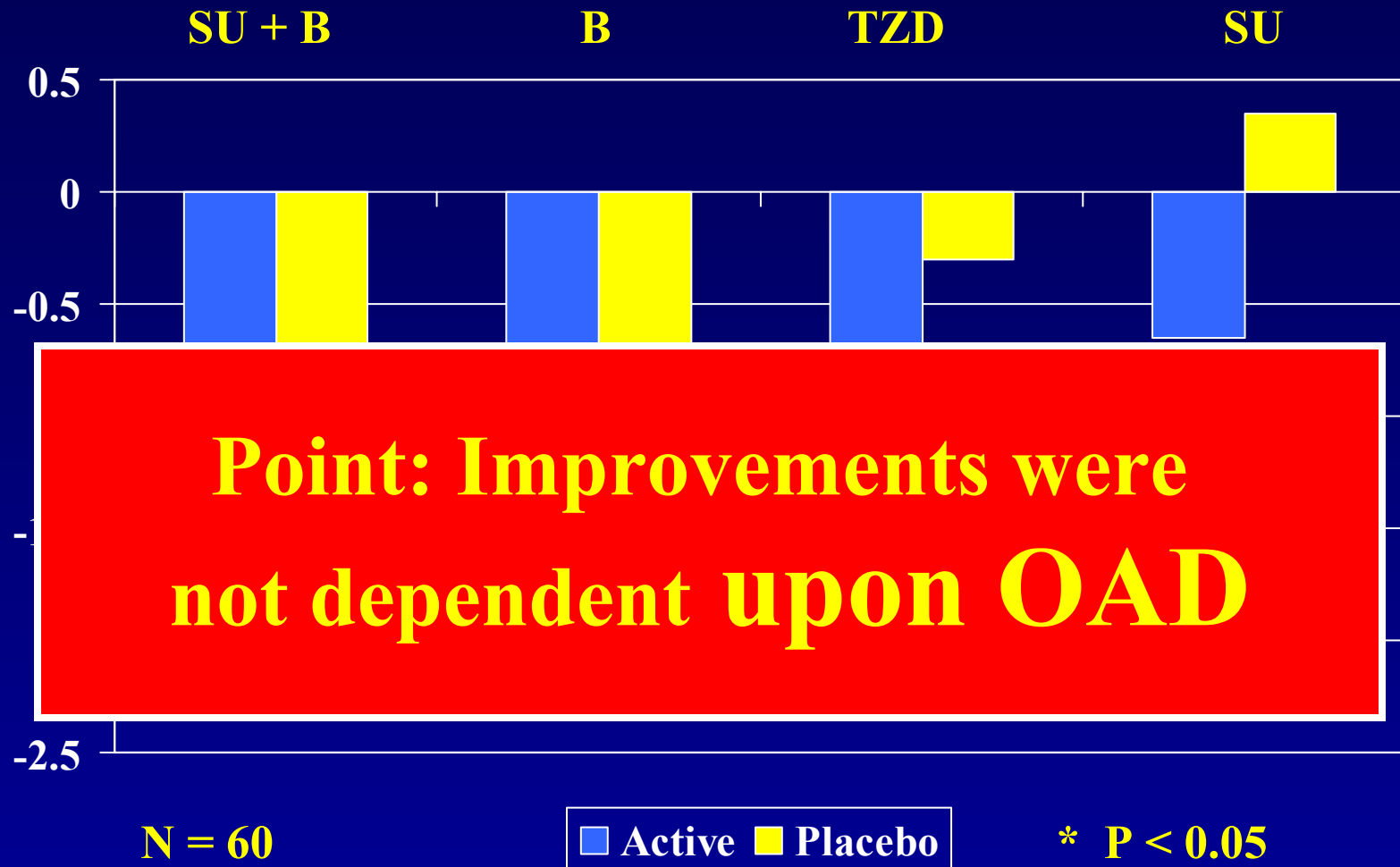
Effect on Total Cholesterol and LDL Cholesterol



“All” = data from all subjects; “TC > 200” = data from subjects with baseline cholesterol >200 mg/dL

Diachrome® Study Results

Subjects with Baseline A1c ≥ 10.0



Diachrome® Study Extension Phase

- 270 Day Extension Phase to 90 Day Study
- All subjects on active intervention
- Visits at 2, 4, 6, and 9 months post enrollment
- 28 subjects enrolled; 24 completed.
- OADs held steady
- No daily insulin use

**Results are positive,
to be presented at ADA June, 2006**

Economic Analysis Model

- Statistical analysis used to estimate a range of potential 3-year cost savings
- Lifetime cost savings estimated by adjusting literature benchmark, and using price index to adjust for inflation



Literature Review of Economic Impact

- Gilmer showed that medical care charges increase for every one percentage point increase in HbA_{1C} above 7 percent. The savings vary depending on level of HbA_{1C} and other “diseases” that the patient may have
- Gilmer estimated that decrease in HbA_{1C} would result in direct cost savings over a three year period:
 - Only diabetes \$ 805
 - Diabetes & Hypertension \$1,130
 - Diabetes & Heart Disease \$2,078
 - Diabetes, Heart & Hypertension \$2,675

Gilmer TP, et. al. The cost to health plans of poor glycemic control. Diabetes care 1997;20:1847-1853

Literature Review of Economic Impact

- Menzin, in a retrospective study, examined the potential short-term economic benefits of improved glycemic control:

<u>Change in Glycemic Control</u> (<u>initial HbA_{1C} to final HbA_{1C}</u>)	<u>Cost Reduction</u> (<u>3-years</u>)
■ Fair to good (8%-10%) to (less than 8%)	\$ 410
■ Poor to fair (10%+) to (8-10%)	\$1,660
■ Poor to good (10%+) to (less than 8%)	\$2,070

Menzin, j. et. Al. Potential short-term economic benefits of improved lycemic control, a managed care perspective. Diabetes Care 2001;24:51-55

Use of Chromium Picolinate and Biotin in the Management of Type 2 Diabetes: An Economic Analysis

JOSEPH P. FUHR, Jr., Ph.D.,^{1,2} HOPE HE, M.A. M.P.A.,² NEIL GOLDFARB, B.A.,²
and DAVID B. NASH, M.D., M.B.A.²

ABSTRACT

This paper addresses the potential economic benefits of chromium picolinate plus biotin (Diachrome[®]) use in people with Type 2 diabetes (T2DM). The economic model was developed to estimate the impact on health care systems' costs by improved HbA_{1C} levels with chromium picolinate plus biotin (Diachrome). Lifetimes cost savings were estimated by adjusting a benchmark from the literature, using a price index to adjust for inflation. The cost of diabetes is highly dependent on the HbA_{1C} level with higher initial levels and higher annual increments increasing the cost. Improvement in glycemic control has proven to be cost-effective in delaying the onset and progression of T2DM, reducing the risk for diabetes-associated complications and lowering utilization and cost of care. Chromium picolinate plus biotin (Diachrome) showed greater improvement of glycemic control in poorly controlled T2DM patients (HbA_{1C} $\geq 10\%$) compared to their better controlled counterparts (HbA_{1C} $< 10\%$). This improvement was additive to that achieved by oral hypoglycemic medications and correlates to calculated levels of cost savings. Average 3-year cost savings for chromium picolinate plus biotin (Diachrome) use could range from \$1,636 for a poorly controlled patient with diabetes without heart diseases or hypertension, to \$5,435 for a poorly controlled patient with diabetes, heart disease, and hypertension. Average 3-year cost savings was estimated to be between \$3.9 billion and \$52.9 billion for the 16.3 million existing patients with diabetes. Chromium picolinate plus biotin (Diachrome) use among the 1.17 million newly diagnosed patients with T2DM each year could deliver lifetime cost savings of \$42 billion, or \$36,000 per T2DM patient. Affordable, safe, and convenient, chromium picolinate plus biotin (Diachrome) could prove to be a cost-effective complement to existing pharmacological therapies for controlling T2DM. (Disease Management 2005;8:265–275)

Economic Analysis: 3- Year Savings Population-wide

Type 2 Diabetes Population-wide Three Year Cost Savings

Number of Type 2 Diabetics	Annual Cost Savings Per Patient	Annual Cost of Diachrome Per Patient	Net Benefit of Use of Diachrome Per Patient	Annual Benefit of Diachrome Use	3 Year Benefit of Diachrome Use
16.3M	\$200	\$120	\$80	\$1.3B	\$3.9B
16.3M	\$500	\$120	\$380	\$6.2B	\$18.6B
16.3M	\$1000	\$120	\$880	\$14.3B	\$52.9B

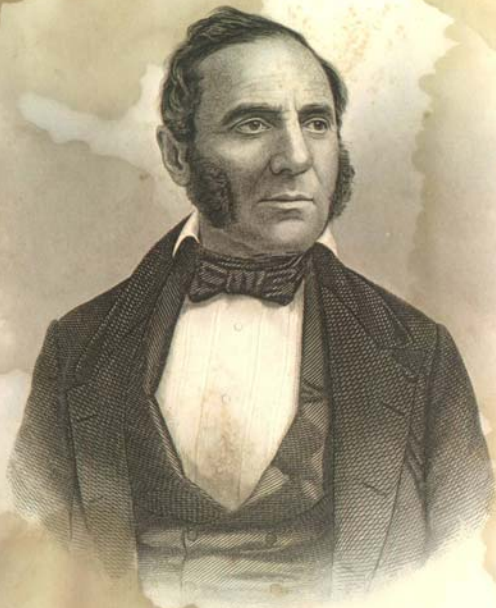
Economic Analysis: Lifetime Cost Savings, Newly Diagnosed

- Approx. 1.3 million people diagnosed each year with diabetes; 90% with type 2
- Using Ginsberg's estimated lifetime cost savings of \$27,000 (\$36,000 in 2004 dollars) per patient with good diabetes control, lifetime cost savings of those diagnosed with T2DM in 2004 calculates to approximately **\$42 billion**

And I have no doubt that thousands are killed by dosing and drugging every year, instead of assisting nature, by exercise, proper diet, change of climate and rest of mind... I have often regretted that physicians did not attend more strictly to this... *however physicians are paid more for their visits and medicines, than for their advice in these matters.*

Dr. Gunn

Perhaps we should finally start to look at nutrient based solutions as an approach to diabetes!



J. C. Gunn M.D.

Author of Gunn's Domestic Medicine or First Aid to Nature.

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