Role of Carnosine in Prevention & Treatment of Obesity and Type 2 Diabetes

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Outline

- Burden and risk factors of obesity and type 2 diabetes
- Carnosine - current evidence
    - animal studies
    - human studies
- Our clinical trials on carnosine and cardiometabolic health
- Conclusions

Burden and risk factors for obesity and type 2 diabetes

Burden of obesity and type 2 diabetes

- 60% of adult Australians overweight or obese
- 22% of Australians > 25 years have prediabetes or type 2 diabetes
- 80% obese patients with type 2 diabetes develop cardiovascular disease
- annual healthcare costs cca 9 billion

Walls, *Obesity* 2012
Chen, *Nat Rev Endocrinol* 2012
Zimmet, *Nature* 2001

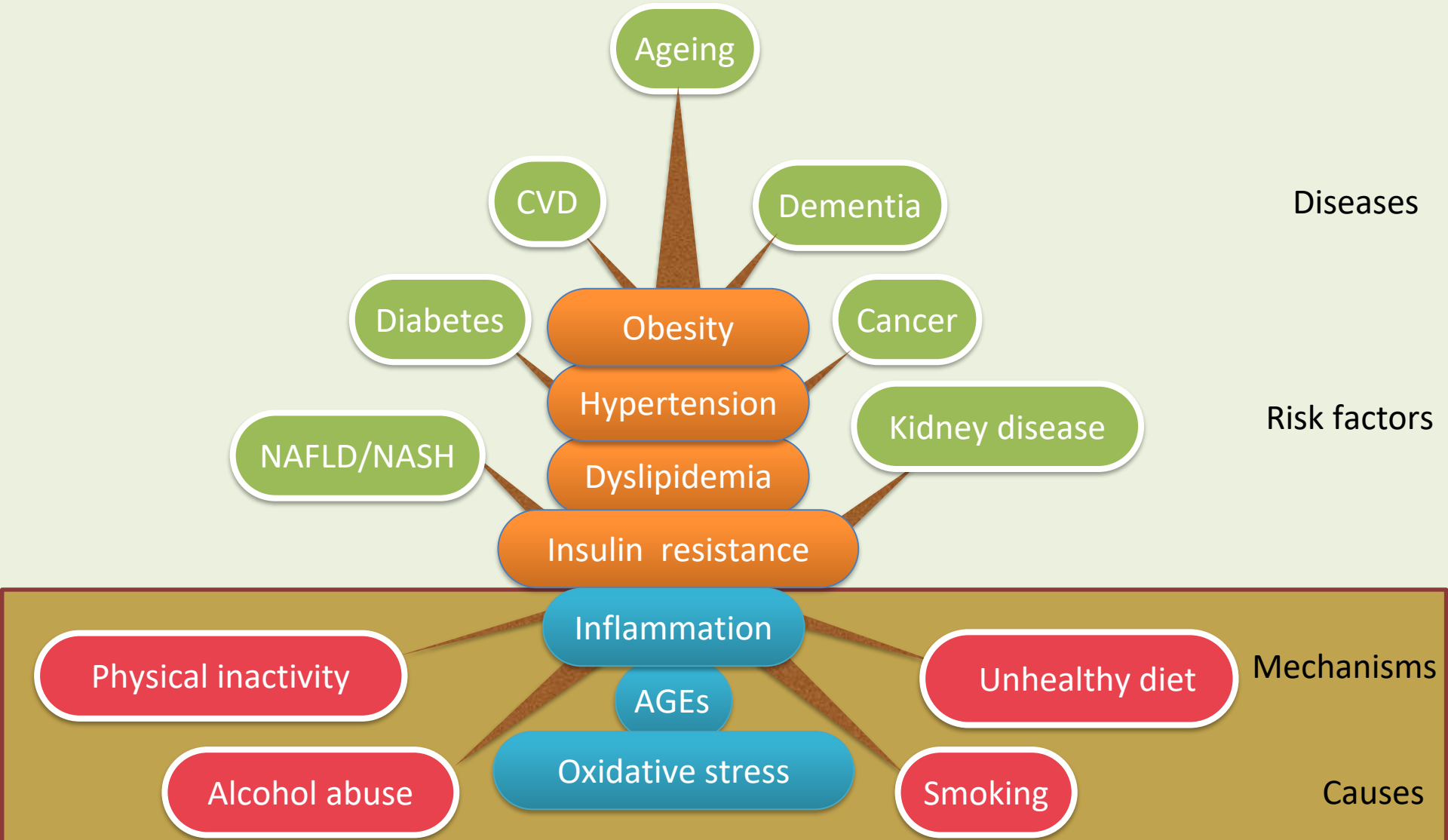
Risk factors for obesity and type 2 diabetes

- multiple risk factors
- shared with other chronic diseases (cardiovascular diseases, dementia, depression, cancer, ageing)
- long latency - amenable to prevention

The ideal preventative strategy/intervention:

- prevents multiple risk factors and therefore diseases
- impacts mechanisms of diseases
    - lifestyle intervention (diet & exercise)
- synergistic with exercise

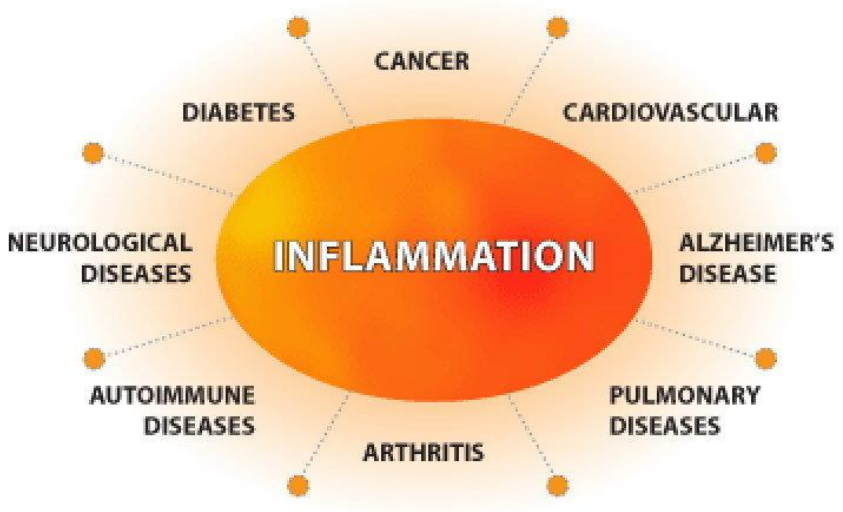
Tree of chronic diseases



My Research Focus

Identifying and providing evidence for interventions applicable for prevention of diabetes and related chronic diseases, that are…

- safe
- low cost
- easily scalable
- immediate public health impact



- diets and supplements
  - cheaper
  - low side effect profile
  - no need for regulatory approval
  - good quality trials are often missing

Why carnosine ?

What is carnosine?

Beta-Alanine L-Histidine

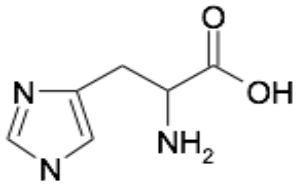
Main dietary sources: 50 to 250 mg/dL

Red meat

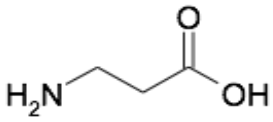
Whale meat

Fish

Histidine

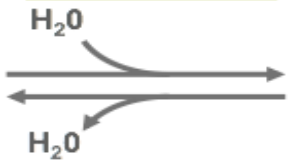


β-Alanine



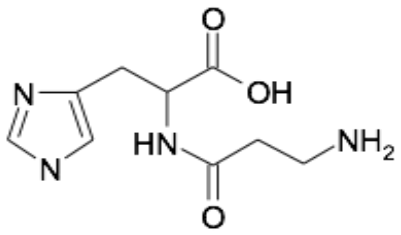
Carnosine-Synthase

H_2O



H_2O

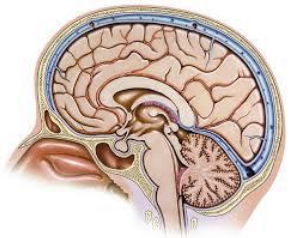
Carnosinase

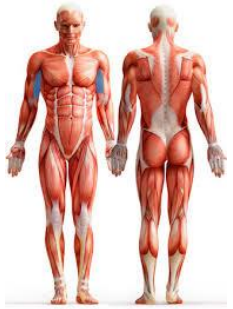


CN1 – plasma
CN2 – gut

What is carnosine?

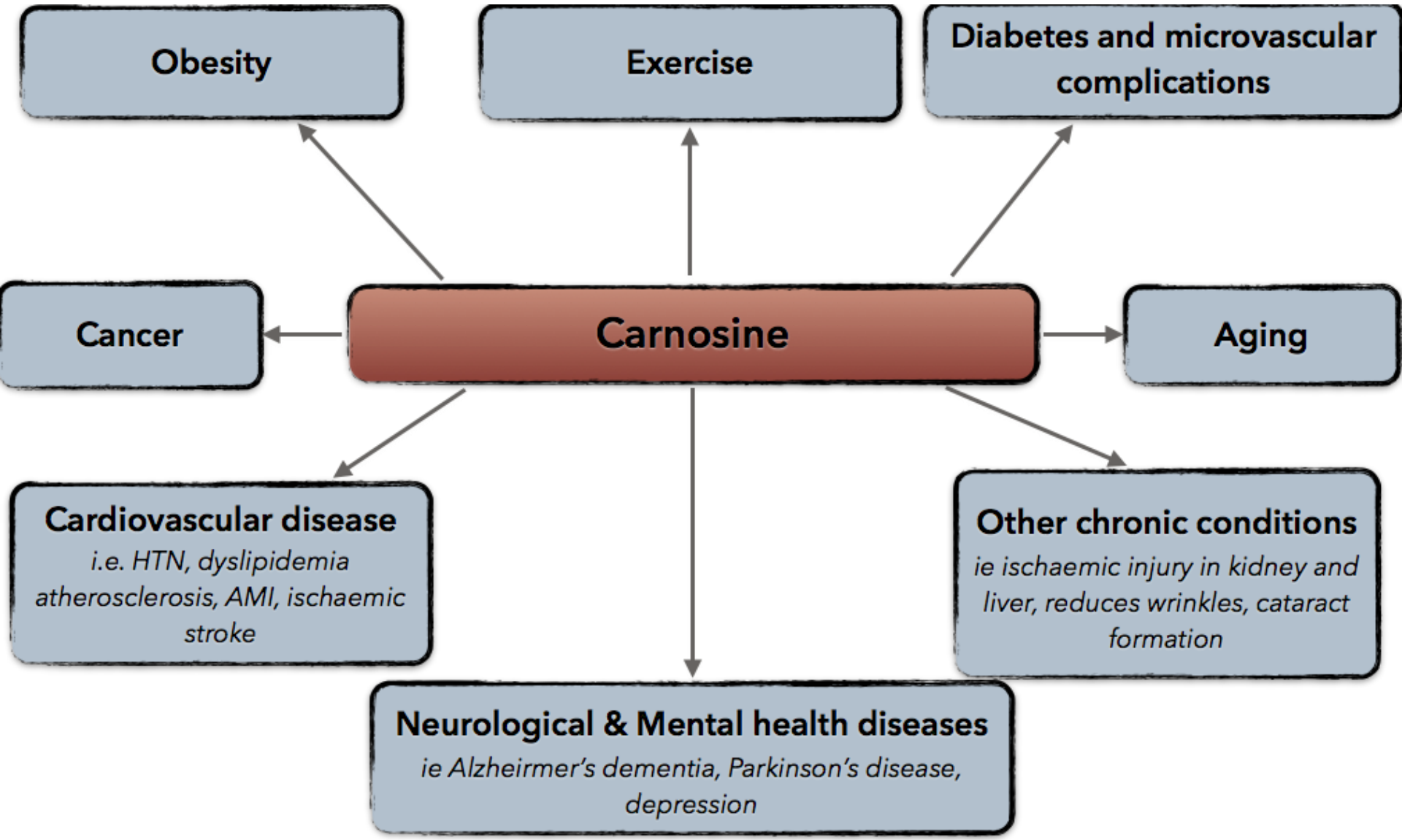
- naturally occurring dipeptide (beta-alanine L-histidine) in humans
  - cardiac & skeletal muscle, brain tissue
  - first described in 1900
  - first appeared around a decade ago - food supplements and skin creams
  - advertised an elixir of youth
  - yet little human research





- carnosine supplement:
  - water soluble powder
  - safe
  - 0.5-3.5g necessary for biological effects
  - low cost (1AUD$ per day)

Carnosine - Magic Bullet for Chronic Diseases?



Mechanism of Action of Carnosine

- ⬇ chronic low-grade inflammation
  Yan, 2009; Tsai, 2010; Lee, 2005

- ⬇ oxidative stress
  Hipkiss, 2011; Ma, 2012

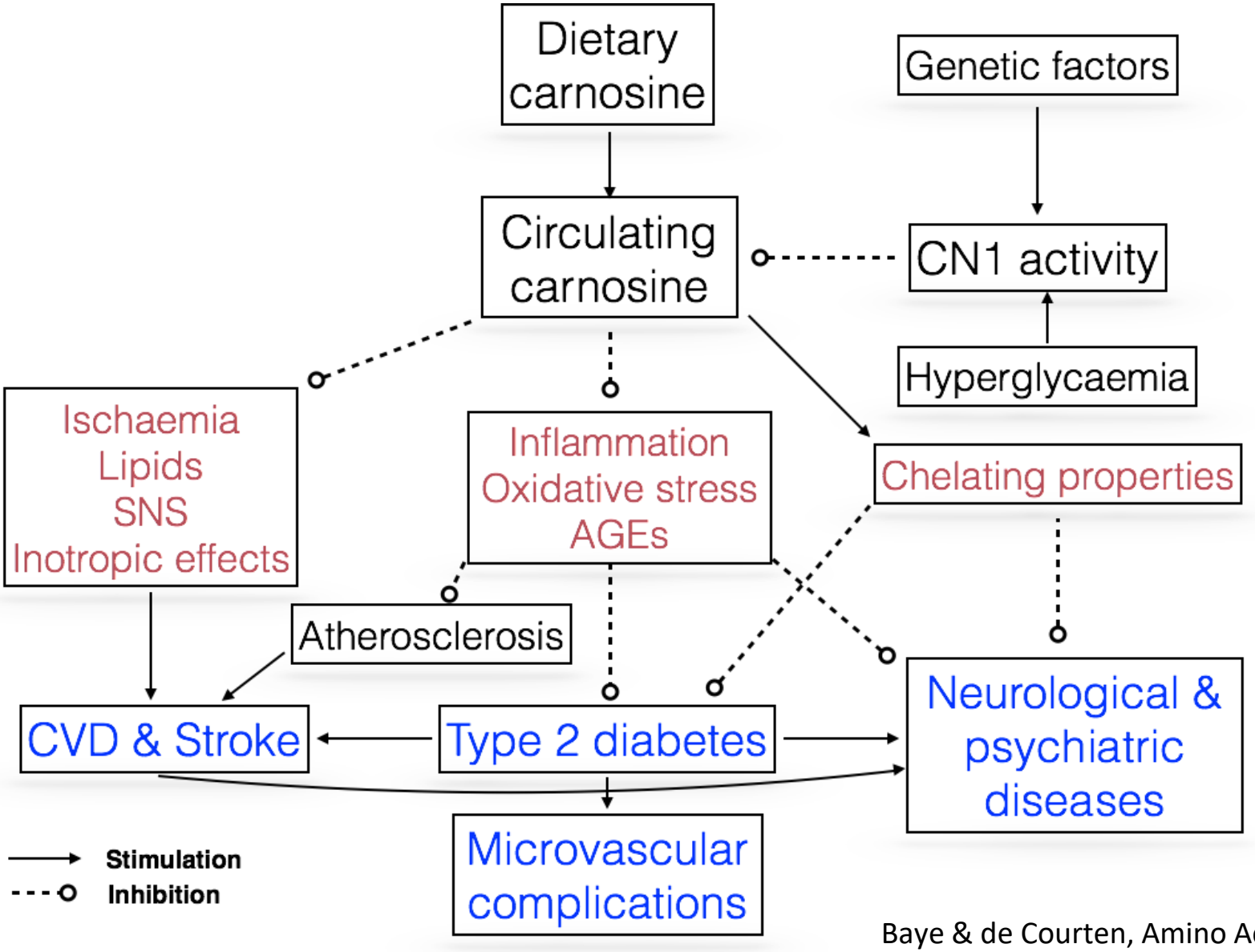
- ⬇ advanced glycation (AGEs)
  Burcham, 2002; Hipkiss, 2002

- chelating properties
  Price, 2001; Arnal, 2011

- ⬇ ischemia
  Doborota, 2005; Fujii, 2005

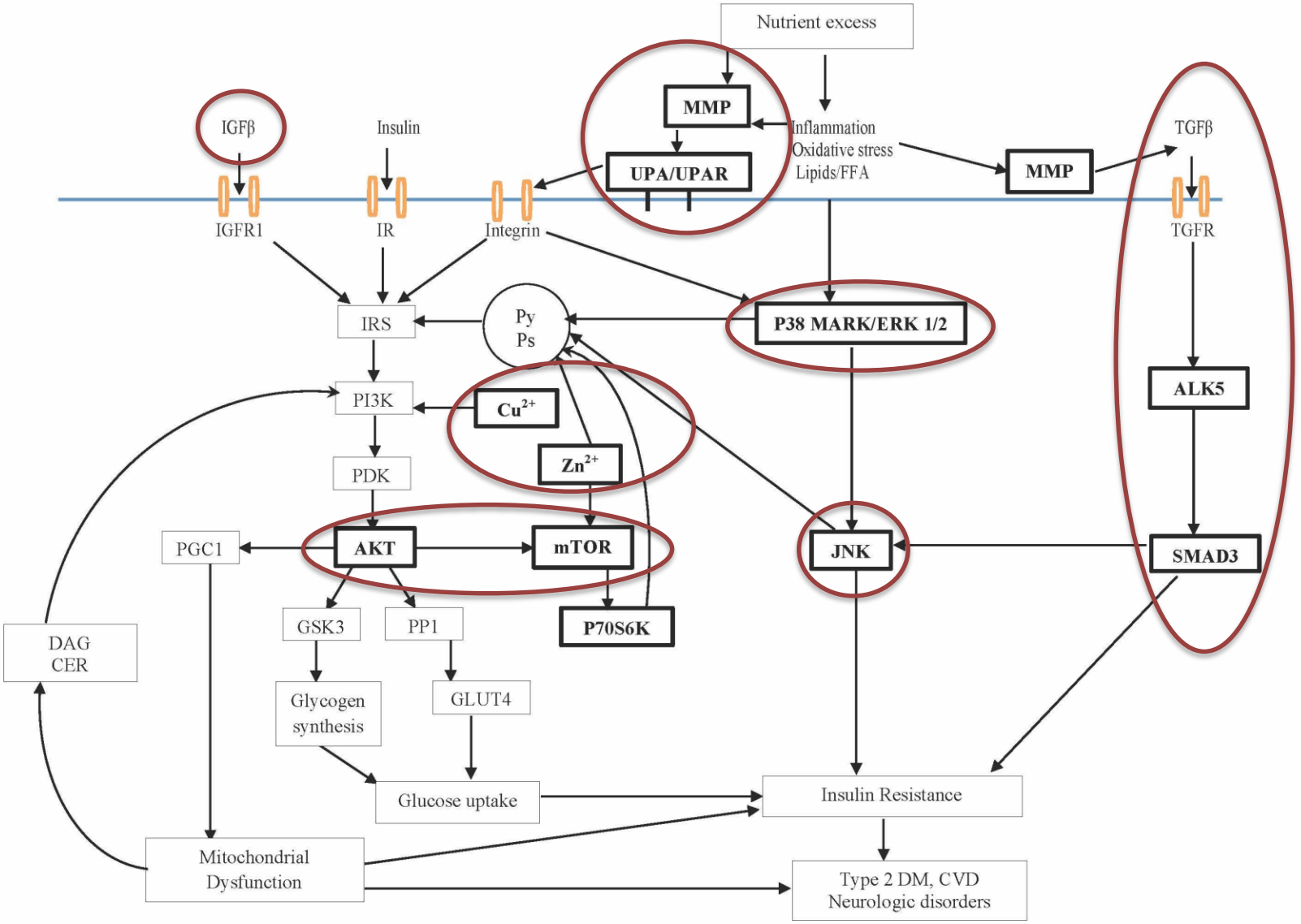
- ⬇ sympathetic nervous system activity
  Nagai, 2012; Horii, 2012

How could it all work?



Baye & de Courten, Amino Acids, 2016

Carnosine & signalling



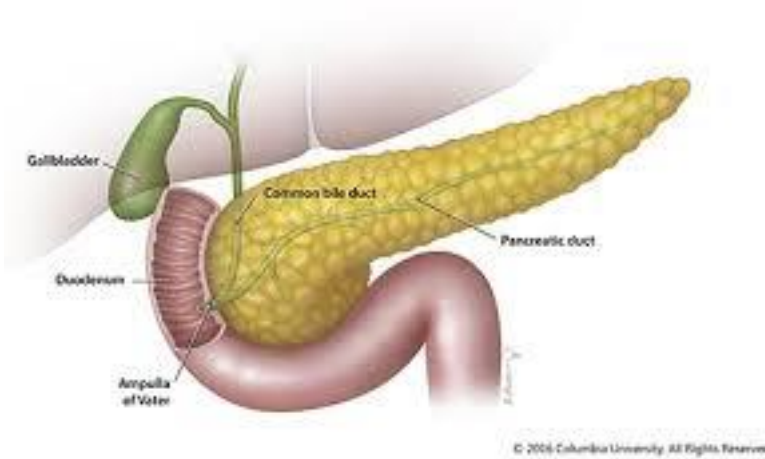
Baye & de Courten, Amino Acids, 2016

Evidence from animal studies

Carnosine, obesity and type 2 diabetes (rodents)

Carnosine reduced

- weight
- insulin levels
- insulin resistance
- delayed development of diabetes
- glucose levels in animals with diabetes
- inflammation and oxidative stress



Aldini G, 2011; Mong, 2011; Sauerhofer, 2007; Lee YT, 2005

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Carnosine and cardiovascular disease (rodents)

Carnosine supplementation reduced

- cholesterol and triglycerides in plasma and liver
- oxidation and glycation of LDL (foam cell formation)
- atherosclerosis
- ischaemic effects

Aldini, 2011; Brown, 2014; Barski, 2013; Mong, 2011; Rashid, 2007; Lee YT, 2005

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Evidence from human studies

Carnosine supplementation improves exercise performance

↑ exercise capacity compared to placebo

- Hobson, 2012 (meta-analysis)

↑ high-intensity anaerobic performance

- Artioli, 2010

Mechanisms

- ↑ muscle buffering capacity, ↓ lactate
  - Swietach, 2014
- improvement in calcium handling and antioxidant capacity
  - Sale, 2013
  - Dutka, 2004

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Health benefits of carnosine supplementation in humans

Health benefits of carnosine	Study design	Daily doses	Duration
Improved balance (foot up and go test) and physical performance in the elderly (Szczesniak et al. 2014)	Randomsied placebo controlled trial	1 g	13 weeks
Improved exercise capacity and time to exhaustion in the elderly (del Favero et al. 2012)	Randomsied placebo controlled trial	3.2 g	12 weeks
Improved exercise capacity and high-intensity exercise greater than 60 s (Hobson et al. 2012)	Meta-analysis	1.79 g (average)	
Reduced fasting insulin Decreased insulin resistance Reduced insulin secretion in healthy overweight and obese humans (De Courten et al. 2015a)	Randomsied placebo controlled trial	2 g	12 weeks
Improved quality of life Increased end-diastolic volume Improved physical performance (as measured by 6 min walk test and VO_{2max}) (Lombardi et al. 2015)	Randomised controlled trial	0.5 g	6 months
Improved cognitive performance			
In young healthy soldiers (Hoffman et al. 2015)	Randomsied placebo controlled trial	6 g	1 month
In elderly individuals (Szczesniak et al. 2014)	Randomsied placebo controlled trial	1 g	13 weeks
Improved neurological symptoms such as leg agility and motor examinations in patients with Parkinson's disease (Boldyrev et al. 2008)	Randomised controlled trial	1.5 g	1 month
Improved the executive function and strategic efficiency Reduced perseverative errors in schizophrenic adults (Chengappa et al. 2012)	Randomsied placebo controlled trial	2 g	3 months
Improved receptive speech, socialisation and behaviour in children with autistic spectrum disorders (Chez et al. 2002)	Randomsied placebo controlled trial	800 mg	8 weeks
Ameliorated cognitive impairment in veterans with Gulf War Illness (Baraniuk et al. 2013)	Randomsied placebo controlled trial	1.5 g	12 weeks

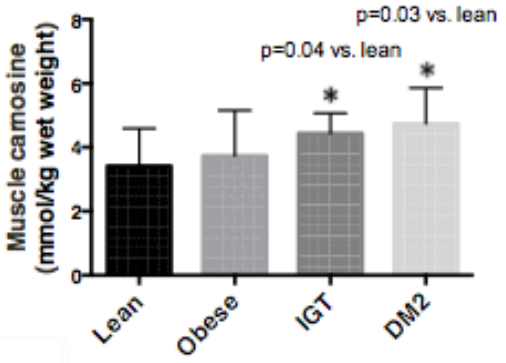
Baye & de Courten, Amino Acids, 2016

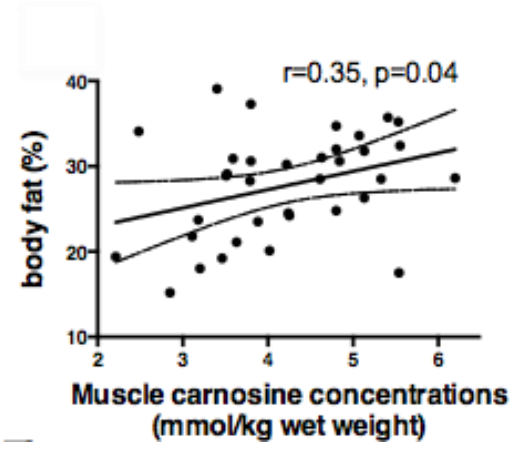
Muscle carnosine content & glucose metabolism (cross-sectional study)

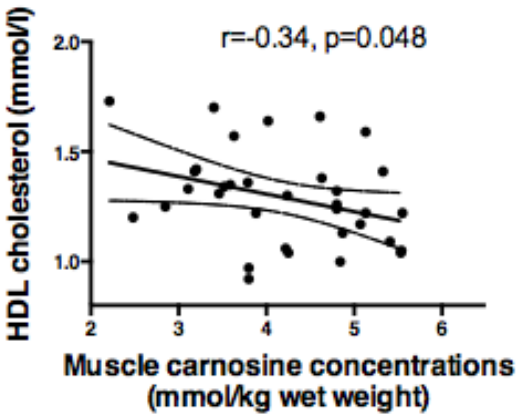
Muscle carnosine increases with worsening

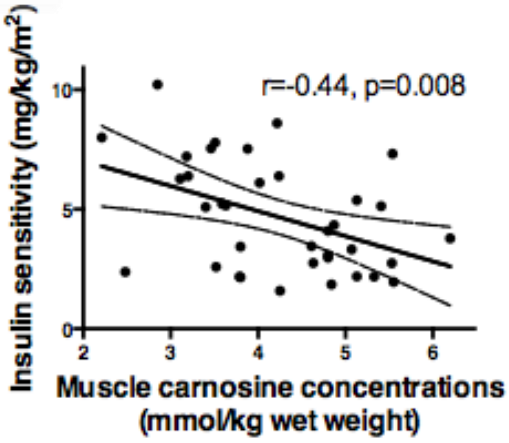
- obesity
- dyslipidemia
- glucose intolerance
- insulin resistance

n=9 lean n=9 obese n=9 IGT n=9 T2DM









de Courten, Ukropcova, PLoS ONE, 2015
Stegen, de Courten, PLoS ONE, 2015

Carnosine & Diabetes

- ↑ muscle carnosine content in drug-naïve patients with type 2 diabetes compared to healthy controls
    - Srikanthan, 2012

- ↓ muscle carnosine levels in patients with type 2 diabetes (on glucose lowering therapy) compared to healthy controls
    - Gualano, 2012

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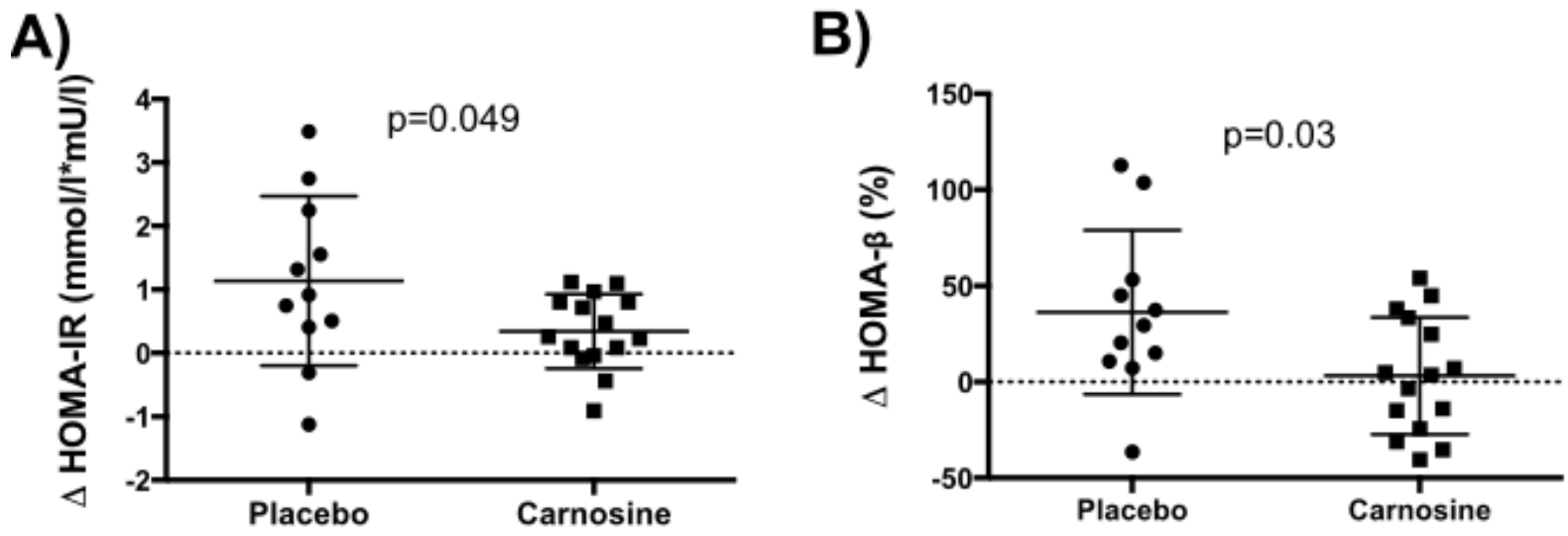
Carnosine supplementation & diabetes risk

RCT: 12-week intervention with 2g/day carnosine vs placebo



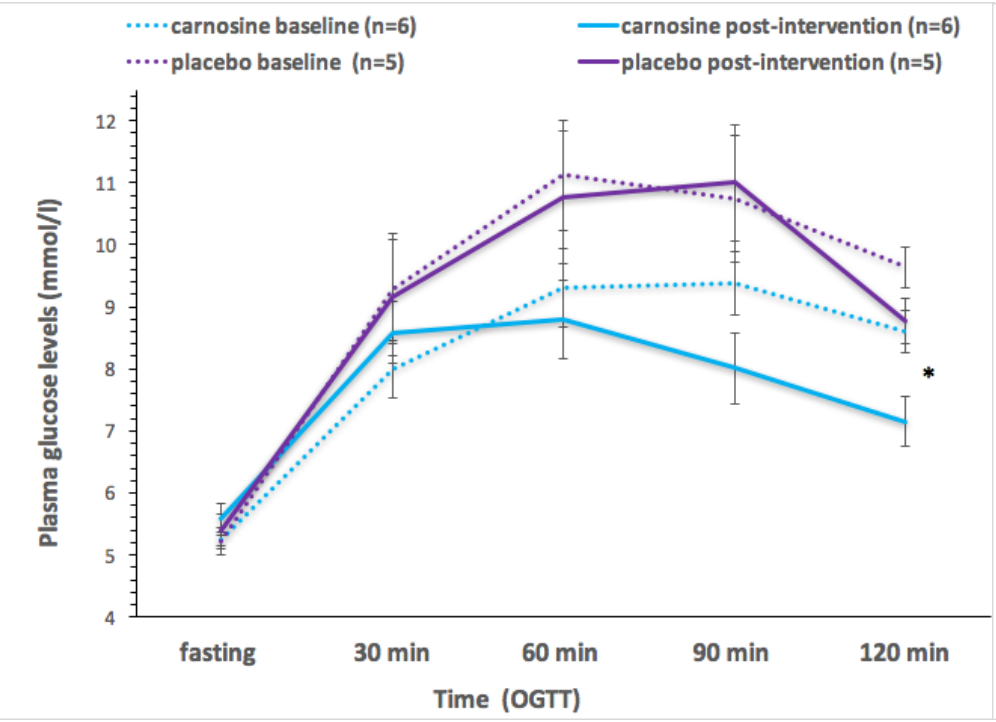
Pilot trial

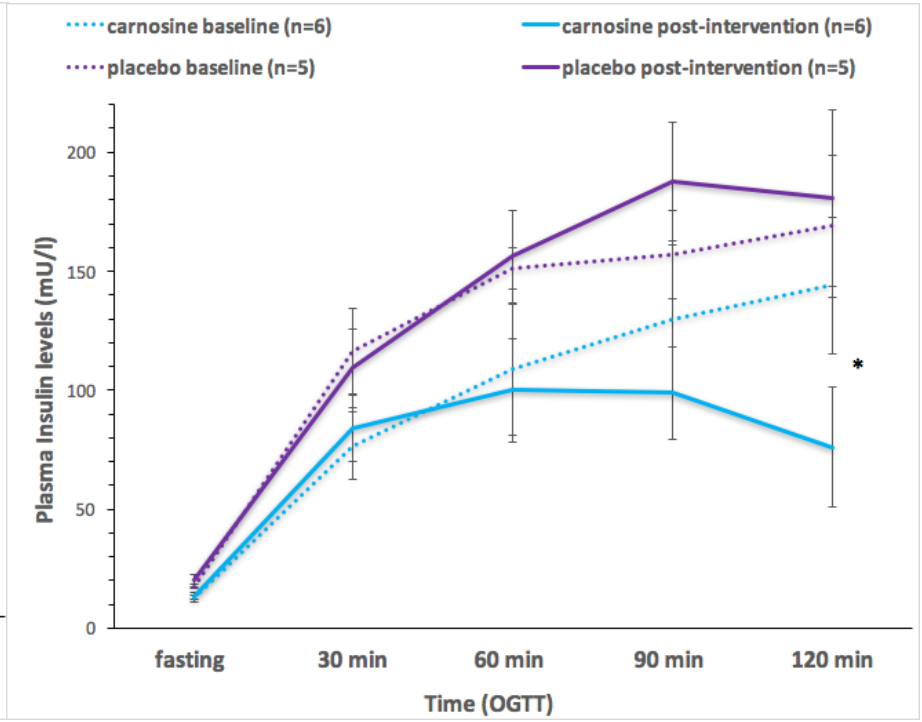
Carnosine supplementation prevents

- **decrease in insulin sensitivity**
- **increase in insulin secretion**
- **no change in inflammation markers**

de Courten et al, Obesity, 2016

Carnosine improves glucose and insulin levels during OGTT in patients with impaired glucose tolerance





* P<0.05

de Courten et al, Obesity, 2016

RCT in patients with prediabetes with carnosine compound

Ingredient	Dietary supplement (Quantity per capsule)	Placebo (Quantity per capsule)
Extract of cinnamon	228.00 mg	-
L-carnosine	100.00 mg	-
Chromium guanylate	1.25 mg (10 μg chromium chloride)	-
Excipients		
Silica	16.00 mg	-
Talc	7.00 mg	7.00 mg
Magnesium stearate	6.00 mg	6.00 mg
Hydrated silica	5.00 mg	5.00 mg
Silicon dioxide	-	16.00 mg
Microcristalline cellulose	-	230.25 mg
Clear transparent HPMC capsule	95.00 mg	95.00 mg
Total	**595 mg**	**496 mg**

N=52, obese individuals with prediabetes
Intervention: 4 months

Liu et al, Plos One, 2015

	Placebo (n = 26)			Dietary supplement (n = 26)			Changes in placebo vs dietary supplement
	Baseline (Day 0)	After treatment (M4)	P value Day 0 *vs.* M4	Baseline (Day 0)	After treatment (M4)	P value Day 0 *vs.* M4	P value
Dietary intake							
Energy (kcal/day)	1989.5±448.5	2045.1±611.1	0.69	1883.8±735.9	1898.6±572.4	0.80	0.90
Carbohydrates (%)	42.8 ±6.7	42.74±7.8	0.96	39.6±7.8	39.3±7.5	0.82	0.91
Proteins (%)	17.6±3.6	17.6±3.8	0.91	17.7±3.9	17.9±3.5	0.69	0.70
Lipids (%)	37.1±5.5	35.7±5.8	0.30	37.9±5.8	37.6±4.5	0.76	0.55
Glucose homeostasis							
FPG (mmol/L) (mmol/L)mmol/L)	6.1±0.6	6.2±0.8	0.36	6.1±0.6	5.9±0.6	0.026	0.020
FP insulin (μU/mL)	9.7±5.7	9.0±4.5	0.77	9.4±3.5	9.9±3.9	0.25	0.33
HbA1c (%)	5.96±0.40	6.12±0.50	0.00015	5.89±0.43	5.99±0.47	0.015	0.32
HOMA-IR	1.3±0.8	1.3±0.6	0.80	1.29±0.5	1.3±0.5	0.31	0.39
HOMA-S (%)	99.7±54.2	99.1±46.6	0.83	95.1±59.3	85.7±34.1	0.31	0.41
HOMA-B (%)	75.0±25.4	68.4±18.4	0.5	72.3±17.6	81.7±19.8	0.043	0.06
Revised QUICKI	0.4±0.1	0.4±0.1	0.29	0.4±0.04	0.38±0.03	0.083	0.66
Disse index	-7.7±6.8	-7.4±6.3	0.76	-6.3±4.5	-7.8±4.5	0.040	0.88
Lipid Homeostasis							
Triacylglycerol (g/L)	1.3±0.5	1.3±0.7	0.52	1.3±0.7	1.3±0.7	0.56	0.91
Total cholesterol (g/L)	2.3±0.5	2.2±0.4	0.36	2.1±0.4	2.1±0.4	0.86	0.49
HDL cholesterol (g/L)	0.5±0.1	0.5±0.2	0.63	0.6±0.2	0.5±0.1	0.12	0.56
LDL cholesterol (g/L)	1.5±0.4	1.45±0.3	0.41	1.4±0.4	1.4±0.5	0.40	0.24
FFA (mmol/L)	0.4±0.2	0.4±0.2	0.11	0.5±0.2	0.5±0.2	0.24	0.96
Adiposity markers							
Body weight (kg)	87.5±13.7	88.6±14.1	0.035	85.8±10.2	86.8±10.2	0.020	0.81
Body mass index (kg/m^2)	31.6 ± 4.5	31.9 ± 4.7	0.035	31.4 ± 3.1	31.8 ± 3.2	0.014	0.79
Fat mass (kg)	33.8±9.0	34.5±9.4	0.041	34.04±7.1	34.0±6.5	0.94	0.26
Fat mass (%)	39.1±6.8	39.7±7.4	0.09	40.6±7.2	40.0±6.5	0.15	0.026
Fat-free mass (kg)	49.6±8.7	49.5±9.0	0.58	47.6±8.7	48.8±8.2	0.003	0.008
Fat-free mass (%)	58.0±6.5	57.4±7.0	0.09	56.6±6.9	57.2±6.2	0.14	0.020
Adipocyte diameter (μm)	111.3±10.5	111.7±10.0	0.82	114.0±7.3	116.6±5.7	0.045	0.18
Adipokines and markers of inflammation							
Leptin (ng/mL)	32.6±24.0	32.6±23.7	0.99	32.0±21.9	32.9±20.9	0.35	0.54
Adiponectin (μg/mL)	5.0±3.5	4.6±2.2	0.63	4.6±2.1	4.7±2.4	0.97	0.83
hs-CRP (mg/L)	5.9±6.8	6.0±8.6	0.30	4.0±4.3	3.7±5.0	0.59	0.59
PAI-1 (ng/mL)	26.5±22.6	32.4±22.5	0.07	25.8±20.0	33.1±22.2	0.11	0.85
IL-6 (pg/mL)	1.9±1.3	1.9±1.6	0.48	1.9±1.3	1.9±1.1	0.92	0.66
Adipokines assayed in adipose tissue							
Adiponectin (pg/mL)	11877±10501	9656 ±8068	0.19	9283 ±6581	9768 ± 6628	0.72	0.38
IL-6 (pg/mL)	576 ± 446	929 ± 1279	0.22	1130 ± 1777	1487.35 ±2120	0.24	0.92
Akt (arbitrary U)	15.2 ± 15.8	16.8 ± 17.5	0.89	9.5 ± 11.5	16.0 ± 15.7	0.23	0.40

Liu et al, Plos One, 2015

Carnosine effects body composition

Variable	Period	L-Carnosine group n = 22	Placebo group n = 22	MD (95% CI)
Weight (kg)	Before	78.8 ± 16.4	77.6 ± 12.4	1.2 (−7.7 to 10.1)
	After	76.6 ± 16.5	77.5 ± 12.7	−0.2 (−0.9 to 0.5)
	MD (95% CI)	−0.2 (−0.7 to 0.1)	−0.1 (−0.6 to 0.4)	
BMI (kg/m^2)	Before	29.1 ± 5.3	28.3 ± 4.6	.7 (−2.2 to 3.7)
	After	29.0 ± 5.3	28.3 ± 4.4	−0.1 (−0.3 to 0.1)
	MD (95% CI)	−0.1 (−0.3 to 0.0)	.0 (−0.2 to 0.2)	
Waist circumference (cm)	Before	100.8 ± 12.1	103.1 ± 10.5	−2.7 (−9.6 to 4.1)
	After	100.3 ± 11.5	103.6 ± 10.1	−0.2 (−1.1 to 0.7)
	MD (95% CI)	−0.5 (−1.2 to 0.2)	−0.5 (−0.2 to 0.2)	
Fat mass (%)	Before	31.0 ± 10.4	31.1 ± 10.3	−0.1 (−6.4 to 6.1)
	After	29.4 ± 10.6	31.0 ± 10.0	−1.5† (−2.3 to −0.5)
	MD (95% CI)	−1.6* (−2.3 to −0.8)	−0.1 (−0.6 to 0.4)	
Fat-free mass (%)	Before	57.2 ± 11.2	55.9 ± 11.0	.7 (−5.4 to 8.1)
	After	58.5 ± 10.7	55.4 ± 11.4	1.7† (0.5 to 2.3)
	MD (95% CI)	1.3* (0.1 to 2.4)	−0.5 (−0.8 to −0.1)	
SBP (mm Hg)	Before	11.7 ± 1.3	11.8 ± 1.2	−0.1 (−0.9 to 0.7)
	After	11.2 ± 1.5	11.6 ± 0.8	−0.3 (−0.8 to 0.2)
	MD (95% CI)	−0.4* (−0.7 to 0.1)	−0.2 (−0.7 to 0.3)	
DBP (mm Hg)	Before	7.7 ± 1.1	7.9 ± 0.8	−0.1 (−0.7 to 0.4)
	After	7.4 ± 0.9	7.6 ± 0.6	−0.1 (−0.6 to 0.4)
	MD (95% CI)	−0.3 (0.7 to 0.1)	2.3 (−0.1 to 0.5)	

44 patients with type 2 diabetes on therapy (Metfromin and Glibeclamide)
Mean age 43 years, duration of diabetes 4.5 years, HBA1c 6-6.5%
Intervention: 12 weeks, 1g Carnosine

Houjeghani, Nutr Res, 2018

Carnosine improves glucose and lipid metabolism

Variables	Period	L-Carnosine group n = 22	Placebo group n = 22	MD (95% CI)	MD (95% CI)
FBS (mg/dL)	Before	137.0 ± 36.1	135.2 ± 25.1	1.7 (−17.3 to 20.8)	–
	After	127.1 ± 21.0	139.0 ± 31.4	−13.7 † (−25.5 to −2.0)	−13.1 ‡ (−25.3 to −0.8)
	MD (95% CI)	−9.9 * (−21.1 to 1.4)	4.6 (−4.1 to 13.3)		
HbA1c (%)	Before	6.5 ± 1.2	6.0 ± 0.8	.5 (−0.1 to 1.1)	–
	After	5.8 ± 0.6	6.1 ± 0.8	−0.6 † (−0.9 to −0.2)	−0.6 ‡ (−0.9 to −0.3)
	MD (95% CI)	−0.7 * (−1.1 to −0.3)	.1 (−0.6 to 0.3)		
Fasting insulin (μIU/mL)	Before	4.7 ± 2.2	4.0 ± 1.9	.6 (−0.5 to 1.9)	–
	After	3.8 ± 1.8	3.7 ± 1.6	−0.6 (−1.6 to 0.4)	−0.4 (−1.1 to 0.4)
	MD (95% CI)	−0.9 * (−1.5 to −0.2)	−0.2 (−0.9 to 0.4)		
HOMA-IR (mmol/μIU/mL)	Before	1.6 ± 0.7	1.3 ± 0.7	.2 (−0.2 to 0.7)	–
	After	1.5 ± 0.7	1.4 ± 0.7	−0.2 (−0.6 to 0.1)	−0.1 (−0.2 to 0.0)
	MD (95% CI)	−0.1 (−0.2 to 0.0)	0.1 (0.0 to 0.1)		
HOMA-β (%)	Before	28.0 ± 18.8	21.3 ± 11.3	6.6 (−3.0 to 1.6)	–
	After	23.5 ± 12.1	20.2 ± 12.5	−0.6 (−6.0 to 5.3)	−0.6 (−6.0 to 4.5)
	MD (95% CI)	−4.4 (−1.0 to 1.0)	−1.1 (−4.3 to 2.1)		
TG (mg/dL)	Before	159.5 ± 57.4	161.7 ± 45.8	−2.2 (−34.3 to 29.5)	–
	After	137.3 ± 48.2	167.8 ± 57.6	−23.1 †(−49.8 to 3.7)	−29.8 ‡ (−52.7 to −6.8)
	MD (95% CI)	−22.1 * (−41.4 to −2.8)	6.1(−7.5 to 19.8)		
TC (mg/dL)	Before	158.6 ± 33.5	153.1 ± 29.2	5.4 (−13.7 to 24.6)	–
	After	159.5 ± 33.9	151.5 ± 30.0	3.7 (−8.9 to 16.3)	2.6 (−9.4 to 14.6)
	MD (95% CI)	.9 (−8.3 to 10.2)	−1.5 (−11.2 to 8.1)		
LDL (mg/dL)	Before	84.7 ± 26.1	80.0 ± 30.4	4.7 (−12.4 to 21.9)	–
	After	86.2 ± 28.2	77.5 ± 24.5	5.7 (−6.7 to 18.1)	4.8 (−7.7 to 17.2)
	MD (95% CI)	1.4 (−6.0 to 8.9)	−2.5 (−15.0 to 10.1)		
HDL (mg/dL)	Before	48.4 ± 9.7	52.7 ± 13.4	−4.3 (−11.4 to 2.8)	–
	After	46.7 ± 6.6	51.3 ± 18.0	−3.7 (−12.0 to 4.5)	−3.7 (−12.2 to 4.9)
	MD (95% CI)	−1.6 (−4.5 to 1.2)	−1.4 (−11.6 to 8.8)		

Values are means ± SD. $P < .05$ was considered significant.
Abbreviation: MD: mean difference.
* Significant within-groups mean difference ($P < .05$; paired Student t test).
† Significant between-groups mean difference ($P < .05$; ANCOVA adjusted for baseline values).
‡ Significant between-groups mean difference ($P < .05$; ANCOVA adjusted for duration of diabetes, changes in energy intake, BMI, and baseline values).

Houjeghani, Nutr Res, 2018

Carnosine lowers advanced glycation end-products

Variables	Period	L-Carnosine group n = 22	Placebo group n = 22	MD (95% CI)	MD (95% CI)
CML (ng/mL)	Before	603.9 ± 87.9	622.0 ± 75.7	−18.2 (−68.3 to 31.4)	–
	After	508.4 ± 89.9	614.8 ± 112.3	−95.8 † (−151.2 to −40.4)	−91.8 ‡ (−148.5 to −35.1)
	MD (95% CI)	−95.5 * (−140.2 to −50.8)	−7.3 (−46.5 to 31.9)		
Pentosidine (ng/mL)	Before	6.8 ± 3.4	4.9 ± 1.8	1.9 § (0.2 to 3.5)	–
	After	3.9 ± 1.9	4.9 ± 2.1	−2.4 †(−4.4 to −0.4)	−2.1 (−4.2 to −0.1)
	MD (95% CI)	−2.8 * (−4.5 to −1.2)	.0 (−.7 to 0.7)		
s-RAGE (ng/mL)	Before	2.9 ± 1.4	2.4 ± 0.8	0.4 (0.3 to 1.1)	–
	After	2.8 ± 1.3	2.2 ± 0.5	0.2 (−.2 to 0.6)	0.4 (−0.1 to 0.8)
	MD (95% CI)	0.1 (−0.3 to 0.5)	−0.1 (−0.3 to 0.1)		

Values are means ± SD.

$P < .05$ was considered significant.

* Significant within-groups mean difference ($P < .05$; paired Student t test).

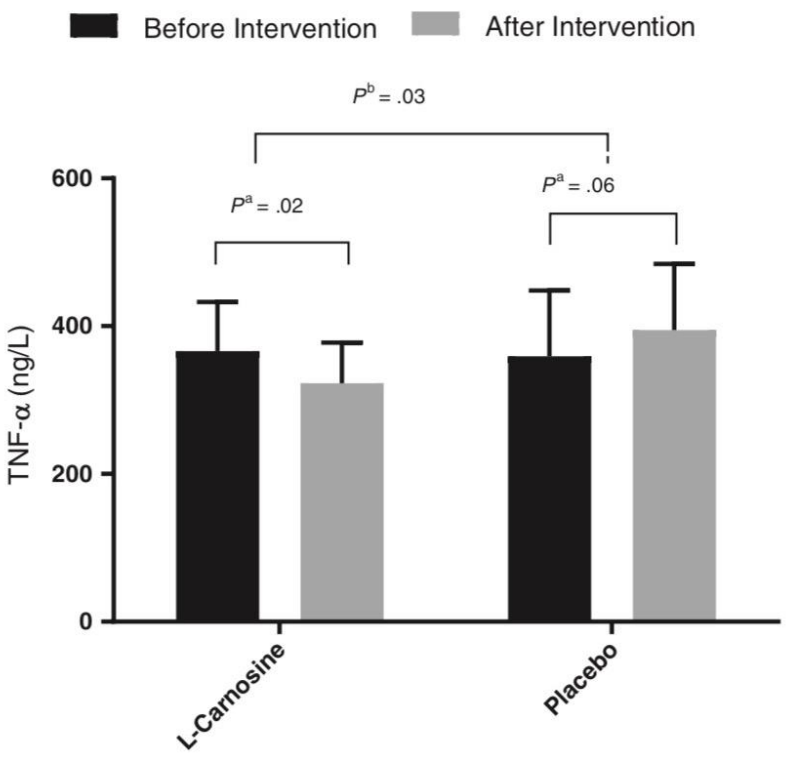
§ Significant between-groups mean difference at baseline ($P < .05$; independent t test).

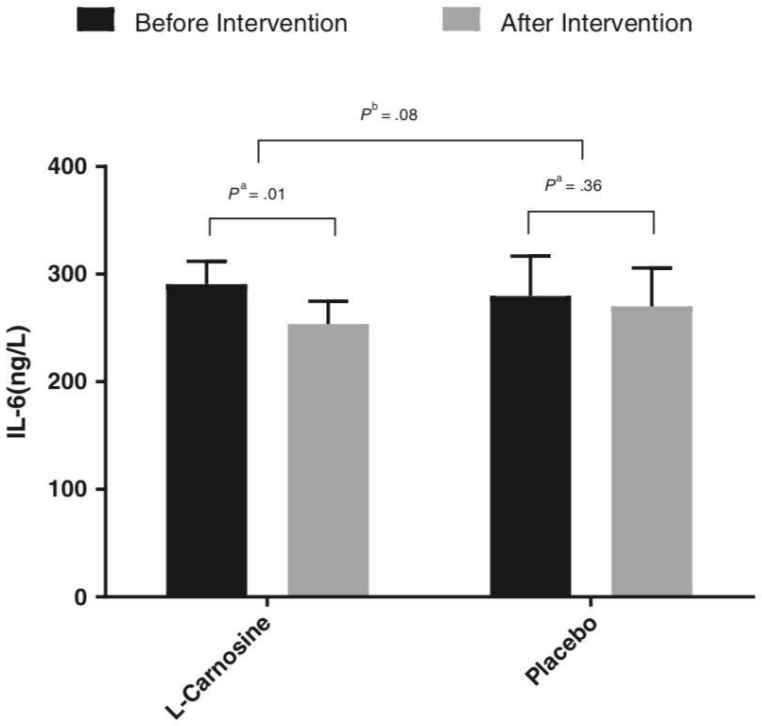
† Significant between-groups mean difference ($P < .05$; ANCOVA adjusted for baseline values).

‡ Significant between-groups mean difference ($P < .05$; ANCOVA adjusted for duration of diabetes, changes in energy intake, BMI, and baseline values).

Houjeghani, Nutr Res, 2018

Carnosine lowers inflammation markers





Houjeghani, Nutr Res, 2018

Carnosine, vit B1 and α-lipoic acid improve obesity and glucose metabolism

N=82, obese sedentary patients with T2DM, mean age 57 years, baseline HbA1c 8.3%
Intervention: 8 week intervention, 6mg/kg body weight (cca 500mg/day)

	Δ(FU − Baseline)	*Δ (%)*	
Glucose, mg/dL	–9.2 ± 6.7	7	↓*
HbA_{1c}, %	–2.3 ± 1.2	28	↓*
Insulin, μIU/mL	3.2 ± 0.7	97	↑*
HOMA-IR	1.01 ± 0.3	72	↑*
HOMA-β	16.8 ± 3.6	112	↑*
QUICKI	–0.03 ± 0.01	8	↓*
Body weight, kg	–2.5 ± 2.5	2.6	↓
BMI, kg/m^2	–0.9 ± 0.9	2.6	↓

Karkabounas, J Med Food, 2018

Carnosine improves HBA1c, lipid profile and renal function patients with type 1 diabetes and nephropathy

N=85, 9-18 year old patients with type 1 diabetes (> 5 years), HbA1c ≤ 8.5%
Intervention: Carnosine 500mg BD, all patients on ACE inhibitor captopril 25 mg daily

	Carnosine				Placebo				
Variable	Baseline (n = 45)	At 12 weeks (n = 43)	Change	P-value[a]	Baseline (n = 45)	At 12 weeks (n = 42)	Change	P-value[a]	P-value[b]
Age (y)	12.4 ± 3.4	-	-	-	13.3 ± 2.8	-	-	-	.173[c]
Males, n (%)	20 (44.4)	-	-	-	23 (51.1)	-	-	-	.527[d]
Disease duration (y)	7.3 ± 2.4	-	-	-	6.7 ± 2.1	-	-	-	.211[c]
Weight SDS	0.04 ± 1.5	0.05 ± 1.7	22.3 ± 12.87	.976	−0.6 ± 1.7	−0.5 ± 1.5	18.8 ± 8.96	.768	.087
Height SDS	−0.2 ± 1.3	−0.1 ± 1.2	41.2 ± 15.65	.706	−0.41 ± 1.18	−0.27 ± 1.3	37.22 ± 14.32	.594	.254
BMI SDS	0.25 ± 1.4	0.36 ± 1.5	44.23 ± 10.32	.720	−0.4 ± 1.7	−0.24 ± 1.5	41.2 ± 8.23	.637	.056
Systolic BP (mmHg)	112.9 ± 13.2	112.9 ± 9.8	1.12 ± 0.89	1.0	110.0 ± 11.1	110.8 ± 11.8	0.88 ± 0.53	.741	.137
Diastolic BP (mmHg)	66.1 ± 7.9	66.7 ± 7.5	0.78 ± 3.55	.713	69.1 ± 6.7	68.3 ± 5.3	−0.81 ± 4.64	.532	.211
Insulin dose (IU/kg/day)	1.1 ± 0.4	1.14 ± 0.4	3.77 ± 1.28	.636	1.16 ± 0.3	1.2 ± 0.3	3.67 ± 1.34	.529	.327
FBG (mg/dL)	147.7 ± 48.9	126.0 ± 34.7	−15.2 ± 9.65	.017	134.5 ± 40.8	151.9 ± 43.0	13.2 ± 8.13	.053	<.001
Triglycerides (mg/dL)	154 ± 21.3	141.5 ± 20.6	−9.3 ± 7.58	.005	148.3 ± 20.7	155 ± 22.1	5.1 ± 3.14	.14	**<.001**
Percentile	90.2 ± 13.5	78.2 ± 11.1	−13.25 ± 4.23	.001	88.6 ± 14.3	90.4 ± 12.7	2.1 ± 0.76	.544	<.001
Total Cholesterol (mg/dL)	186.5 ± 32.4	169.1 ± 31.2	−9.65 ± 6.75	.011	193.5 ± 33. 1	188.6 ± 32.7	−2.67 ± 1.44	.481	.002
Percentile	88.4 ± 15.5	65.7 ± 11.8	−26.3 ± 7.96	<.001	92.2 ± 14.6	87.4 ± 14.1	−5.22 ± 1.23	.486	<.001
HDL cholesterol (mg/dL)	41.2 ± 6.1	52.2 ± 7.5	27.33 ± 13.45	<.001	43.5 ± 6.7	41.6 ± 6.9	−4.44 ± 4.19	.188	<.001
Percentile	5.7 ± 1.2	25.3 ± 8.6	70.6 ± 4.3	<.001	5.8 ± 1.5	5.3 ± 1.1	−8.62 ± 0.17	.431	<.001
HbA1c (%)	8.2 ± 2.1	7.4 ± 1.3	−9.88 ± 7.12	.032	8.0 ± 1.8	8.3 ± 2.4	3.89 ± 2.28	.504	.005
HbA1c (mmol/mol)	65.4 ± 7.3	55.7 ± 6.7	−14.9 ± 7.28	<.001	62.9 ± 6.5	64.2 ± 7.3	2.28 ± 1.18	.375	<.001
Serum creatinine (mg/dL)	0.58 ± 0.1	0.54 ± 0.1	−7.3 ± 6.25	.161	0.56 ± 0.1	0.53 ± 0.1	−5.44 ± 4.17	.158	.425
UACR (mg/g creatinine)	91.7 (56 – 136.5)	38.5 (15 – 50.5)	−58.73 ± 12.35	<.001	74.5 (40 – 110.5)	50.3 (39.5–115)	−32.7 ± 11.13	.713	.002
Alpha 1-microglobulin (mg/L)	16.5 ± 6.8	9.3 ± 6.6	−44.2 ± 10.34	<.001	15.5 ± 7.1	16.8 ± 6.9	8.44 ± 3.17	.381	<.001
TAC (mmol/L)	2.6 ± 0.7	3.4 ± 1.0	30.9 ± 12.24	<.001	2.8 ± 0.8	2.9 ± 0.7	3.83 ± 1.77	.530	.002
MDA (nmol/mL)	25.5 ± 8.1	18.2 ± 7.7	−28.71 ± 10.27	<.001	25.8 ± 8.5	27.0 ± 7.7	4.8 ± 1.18	.485	<.001
Serum carnosine (ng/mL)	106.2 ± 11.7	910 ± 24.1	757.2 ± 115.87	<.001	111.4 ± 18.6	120.2 ± 25.2	8.2 ± 2.66	.104	<.001

Abbreviations: BMI, body mass index; BP, blood pressure; FBG, fasting blood glucose; HbA1c, hemoglobinA1c; HDL cholesterol, high-density lipoprotein cholesterol; MDA, malondialdehyde; SDS, standard deviation score; TAC, total antioxidant capacity; UACR, urinary albumin creatinine ratio.

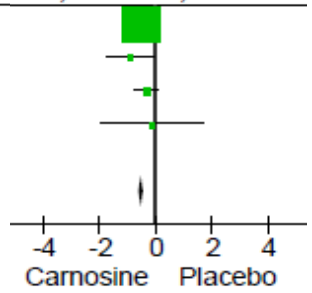
Elbarbary, Pediatric Diabetes, 2017

Carnosine reduced HBA1c and Triglycerides

HbA1c (n=283): MD (95%CI): -0.49% (-0.60, -0.38), p<0.001

Study or Subgroup	Carnosine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Derosa, et al., 2016	7.2	0.3	53	7.7	0.3	49	90.8%	-0.50 [-0.62, -0.38]
Elbarbary et al., 2017	7.4	1.3	43	8.3	2.4	42	1.8%	-0.90 [-1.72, -0.08]
Houjeghani et al., 2017	5.8	0.6	22	6.1	0.8	22	7.1%	-0.30 [-0.72, 0.12]
Liu et al., 2015	5.99	4.7	26	6.12	0.5	26	0.4%	-0.13 [-1.95, 1.69]
Total (95% CI)			**144**			**139**	**100.0%**	**-0.49 [-0.60, -0.38]**

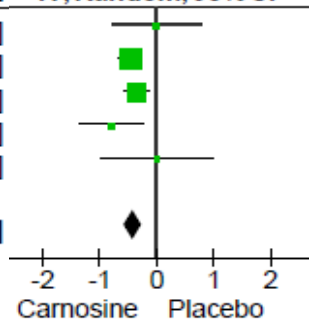
Heterogeneity: Tau² = 0.00; Chi² = 1.93, df = 3 (P = 0.59); I² = 0%
Test for overall effect: Z = 8.68 (P < 0.00001)



Triglycerides (n=265): MD (95%CI): -0.42 mmol/L (-0.57;-0.27), p<0.001

Study or Subgroup	Carnosine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
de Courten et al., 2016	1.7	1	15	1.7	1	11	3.6%	0.00 [-0.78, 0.78]
Derosa, et al., 2016	2.5	0.51	53	2.97	0.57	49	48.0%	-0.47 [-0.68, -0.26]
Elbarbary et al., 2017	3.66	0.53	43	4.01	0.57	42	39.1%	-0.35 [-0.58, -0.12]
Houjeghani et al., 2017	3.56	1.25	22	4.35	0.49	22	7.0%	-0.79 [-1.35, -0.23]
Liu et al., 2015	3.37	1.81	26	3.37	1.81	26	2.3%	0.00 [-0.98, 0.98]
Total (95% CI)			**159**			**150**	**100.0%**	**-0.42 [-0.57, -0.27]**

Heterogeneity: Tau² = 0.00; Chi² = 4.05, df = 4 (P = 0.40); I² = 1%
Test for overall effect: Z = 5.50 (P < 0.00001)



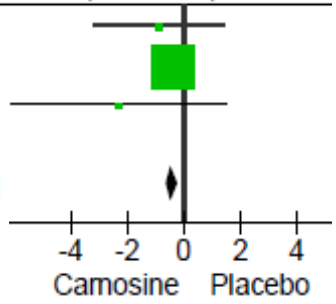
Menon…de Courten, unpublished

Carnosine reduces inflammation and oxidative stress

hsCRP (n=184): MD (95%CI): -0.41 mg/L (-0.62, -0.20), p<0.001

	Carnosine			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
de Courten et al., 2016	2.5	2.3	15	3.4	4	15	0.8%	-0.90 [-3.24, 1.44]
Derosa, et al., 2016	1.8	0.3	53	2.2	0.7	49	98.9%	-0.40 [-0.61, -0.19]
Liu et al., 2015	3.7	5	26	6	8.6	26	0.3%	-2.30 [-6.12, 1.52]
Total (95% CI)			**94**			**90**	**100.0%**	**-0.41 [-0.62, -0.20]**

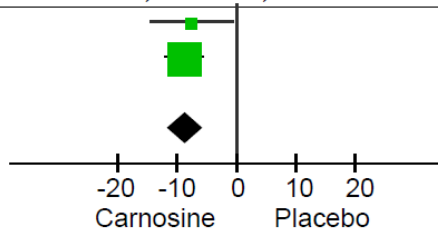
Heterogeneity: Tau² = 0.00; Chi² = 1.12, df = 2 (P = 0.57); I² = 0%
Test for overall effect: Z = 3.81 (P = 0.0001)



Malondialdehyde (Follow Up) (n=184): MD:-8.59 nmol/ml (-11.56,-5.62), p<0.001

	Carnosine			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Derosa, et al., 2016	33.9	14.8	53	41.5	20.8	49	17.7%	-7.60 [-14.66, -0.54]
Elbarbary et al., 2017	18.2	7.7	43	27	7.7	42	82.3%	-8.80 [-12.07, -5.53]
Total (95% CI)			**96**			**91**	**100.0%**	**-8.59 [-11.56, -5.62]**

Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0%
Test for overall effect: Z = 5.67 (P < 0.00001)



Menon… de Courten, unpublished

Carnosine - Summary

MCHRI
Monash Centre for Health Research and Implementation

- food supplement
- safe
- water soluble and easy to mix in foods
- anti-inflammatory, anti-oxidative, anti-AGE, chelating properties and effects on SNS
- all effects are important for many chronic diseases
- ?additive effect with exercise
- compelling evidence from animal studies (2000 animal studies)
- paucity of human data
- need for well designed clinical trials if proven beneficial - potential use for primary prevention many chronic diseases as well as add-on to standard therapy

Gaps in the evidence

Different doses

Mixed supplements

Different populations

Lack of gold-standard methods

Carnosine supplementation in overweight and obese individuals and patients with IGT and type 2 diabetes

Hypothesis

We hypothesise that carnosine supplementation in overweight and obese individuals (Study 1) and patients with IGT and T2DM (Study 2) will improve:

- diabetes risk factors (Study 1) or glycaemic control (Study 2)
- cardiovascular risk factors
- cognitive outcomes

and this will be modulated by reduction in chronic low-grade inflammation, oxidative stress and circulating AGE levels.

Participants & Methods

- **participants:**
  - 84 overweight and obese individuals (Study 1)
  - 52 adult patients with impaired glucose tolerance and T2DM (Study 2)

- **design**: double blind placebo randomised controlled trials
- **intervention**: 1g carnosine BD or matching placebo
- **length of intervention**: 14 weeks
- **measurements**: before and after intervention

Inclusion criteria

- Study 1:
  - Overweight and obese individuals
  - Age 18-60 years
- Study 2:
  - Patients with IGT or T2DM (diet controlled and on Metformin only)
  - Age 18-70 years
  - Stable dose of metformin for least 3 months

- No significant change in weight in last 6 months
- No intention to loose weight during the course of the study

Exclusion criteria

- HbA1c level > 8% for patients with diabetes
- Morbid obesity (>40 kg/m2) - DEXA limitation
- Taking other glucose lowering medications than metformin including injectables
- Taking regular anti-inflammatory medications or supplements potentially effecting glucose metabolism
- current smoker or high alcohol/recreational drug use

Exclusion criteria

- Significant other chronic diseases and psychiatric disorders
- Presence of acute inflammation
- Pregnant or lactating
- Not speaking English (need to complete cognitive function tests - time)

Outcomes

Obesity

- % body fat
- FFM
- IMAT
- Steatosis
- Diet
- Exercise

Diabetes

- insulin sensitivity
- insulin secretory function
- glucose tolerance
- ACR

CVD

- Lipids, lipidomics
- arterial stiffness
- blood pressure / cBP
- endothelial function
- HRV

Cognition

- CANTAB+
- depression
- sleep

-inflammation in plasma and PBMC, oxidative stress, advanced glycation and lipidoxidation end products

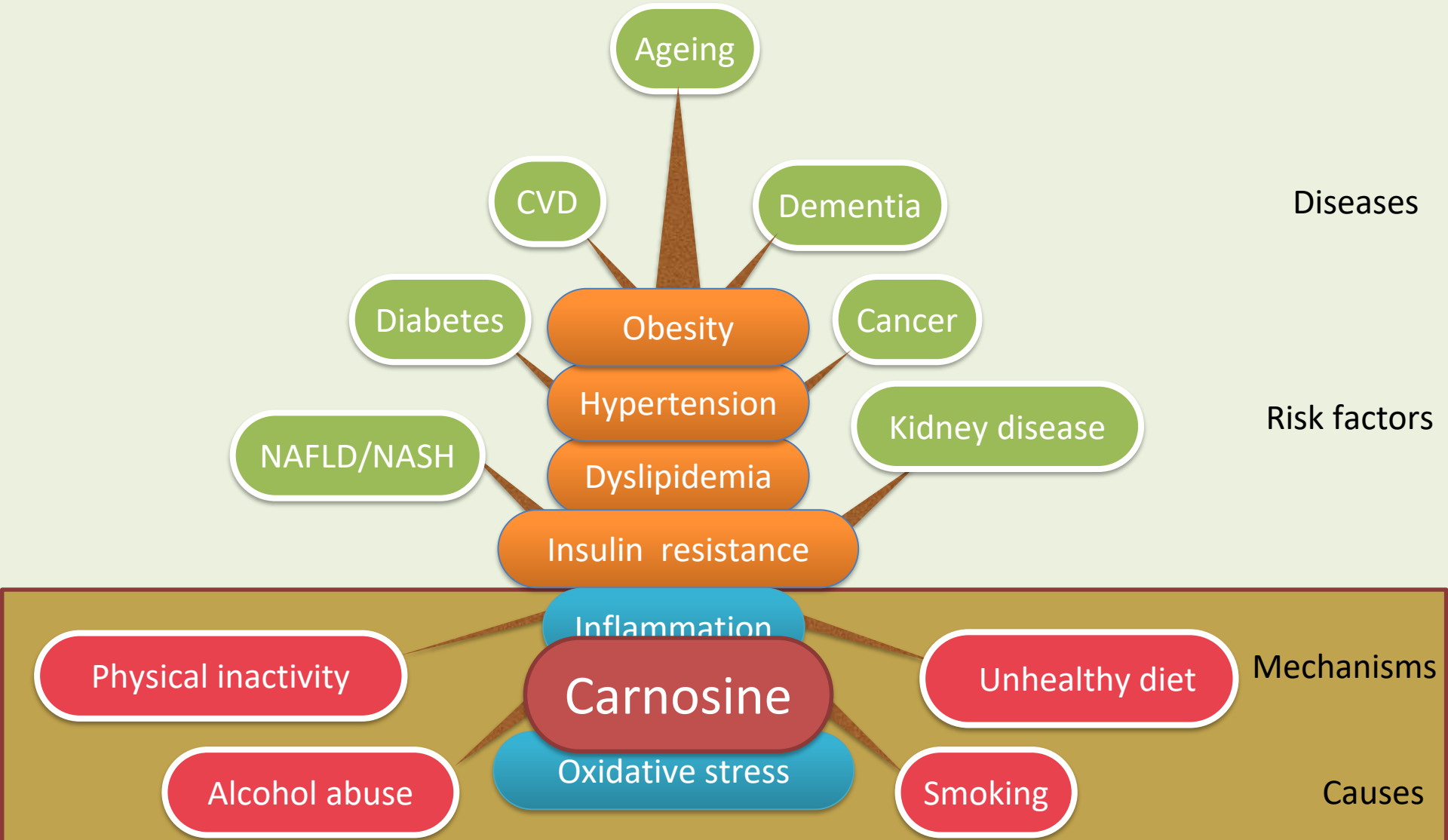
-signalling muscle tissue

-microbiome

-DNA – ageing markers ie telomere length, telomerase

MCHRI
Monash Centre for Health Research and Implementation

Tree of chronic diseases



Conclusions

Carnosine:

- **cheap**
- **low side effect profile**
- **? additive effect with exercise**
- **no need for regulatory approval**

- **good quality RCTs needed to show IF there is health benefit**
- **IF it effects mechanisms which are applicable to several chronic diseases**

Interested to do PhD?

- What you will learn:
  - Systematic review and meta-analysis
  - Clinical trial methodology
  - Gold standard methodologies for assessment of diabetes and cardiovascular risk factors
  - Health economic analyses
  - Average number publications in a PhD is 15

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