钙与肥胖、胆固醇关系研究

李　雪
（哈尔滨医科大学营养与食品卫生教研室）

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哈尔滨医科大学 营养与食品卫生教研室

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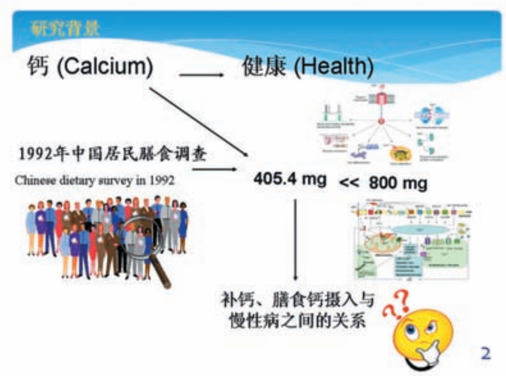
Harbin Medical University



研究背景

钙 (Calcium) —— 健康 (Health)

1992年中国居民膳食调查
Chinese dietary survey in 1992

405.4 mg << 800 mg

补钙、膳食钙摄入与慢性病之间的关系

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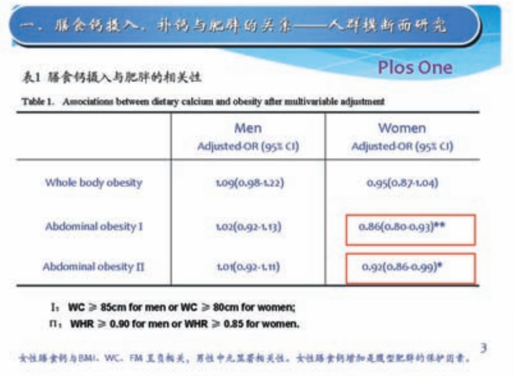

一、膳食钙摄入、补钙与肥胖的关系——人群横断面研究

Plos One

表1 膳食钙摄入与肥胖的相关性

Table 1. Associations between dietary calcium and obesity after multivariable adjustment

	Men Adjusted-OR (95% CI)	Women Adjusted-OR (95% CI)
Whole body obesity	1.09(0.98-1.22)	0.95(0.87-1.04)
Abdominal obesity I	1.02(0.92-1.13)	0.86(0.80-0.93)**
Abdominal obesity II	1.01(0.92-1.11)	0.92(0.86-0.99)*

Ⅰ：WC ≥ 85cm for men or WC ≥ 80cm for women;
Ⅱ：WHR ≥ 0.90 for men or WHR ≥ 0.85 for women.

女性膳食钙与BMI、WC、FM呈负相关，男性中无显著相关性。女性膳食钙增加是腹型肥胖的保护因素。

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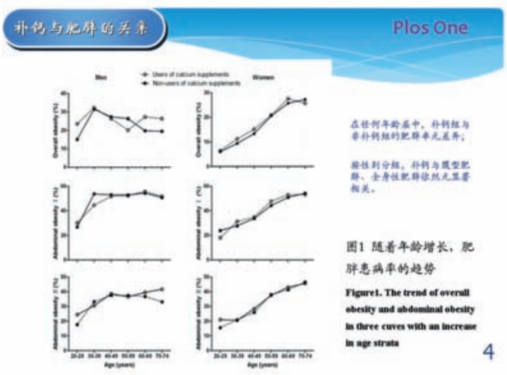

补钙与肥胖的关系

Plos One

在任何年龄层中，补钙组与非补钙组的肥胖率无差异；

按性别分组，补钙与腹型肥胖、全身性肥胖依然无显著相关。

图1 随着年龄增长，肥胖患病率的趋势

Figure1. The trend of overall obesity and abdominal obesity in three cuves with an increase in age strata

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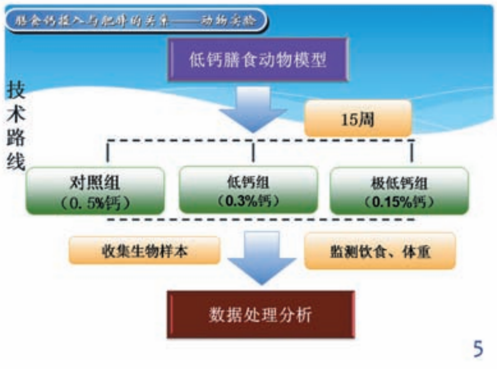

膳食钙摄入与肥胖的关系——动物实验

技术路线

低钙膳食动物模型

15周

对照组（0.5%钙）
低钙组（0.3%钙）
极低钙组（0.15%钙）

收集生物样本
监测饮食、体重

数据处理分析

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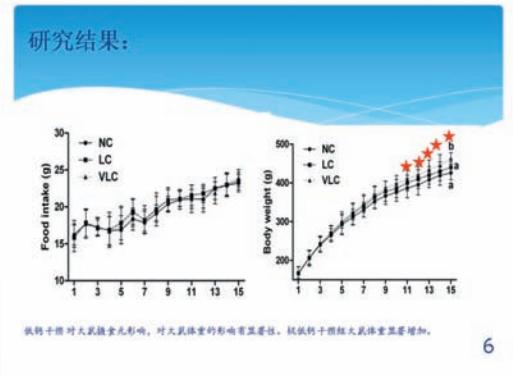

研究结果：

低钙干预对大鼠摄食无影响，对大鼠体重的影响有显著性，极低钙干预组大鼠体重显著增加。

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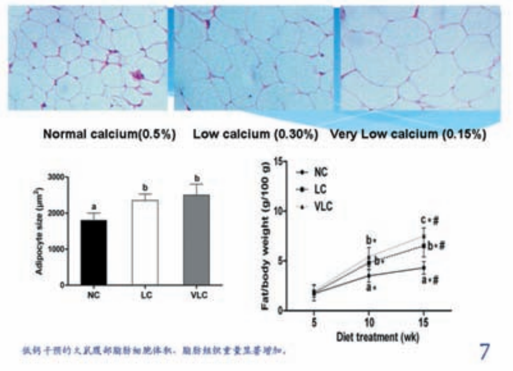

低钙干预的大鼠腹部脂肪细胞体积、脂肪组织重量显著增加。

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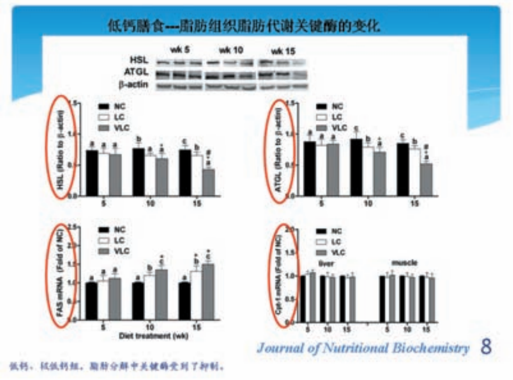
低钙膳食---脂肪组织脂肪代谢关键酶的变化

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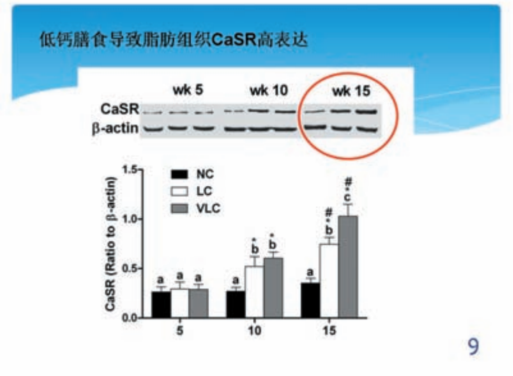
低钙、极低钙组，脂肪分解中关键酶受到了抑制。


低钙膳食导致脂肪组织CaSR高表达

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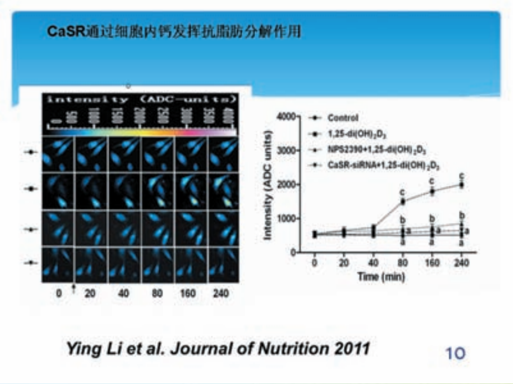
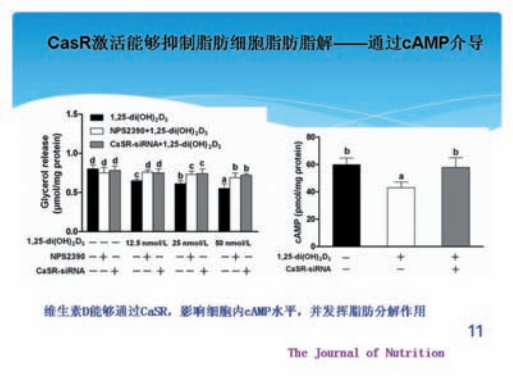

CaSR通过细胞内钙发挥抗脂肪分解作用

Ying Li et al. Journal of Nutrition 2011 10


CasR激活能够抑制脂肪细胞脂肪脂解——通过cAMP介导

维生素D能够通过CaSR，影响细胞内cAMP水平，并发挥脂肪分解作用

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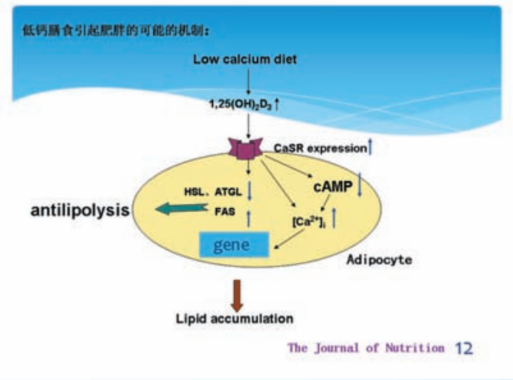
The Journal of Nutrition


低钙膳食引起肥胖的可能的机制：
Low calcium diet
1,25(OH)₂D₃ ↑
CaSR expression ↑
HSL、ATGL ↓
FAS ↑
cAMP ↓
[Ca²⁺]ᵢ ↑
gene
antilipolysis
Adipocyte
Lipid accumulation

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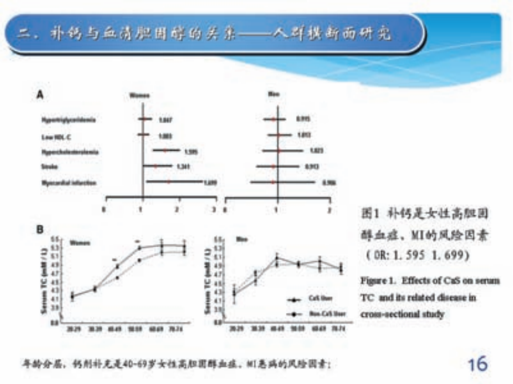
二、补钙与血清胆固醇的关系——人群横断面研究

图1 补钙是女性高胆固醇血症、MI的风险因素（OR: 1. 595 1. 699）

Figure 1. Effects of CaS on serum TC and its related disease in cross-sectional study

年龄分层，钙剂补充是40-69岁女性高胆固醇血症、MI患病的风险因素；

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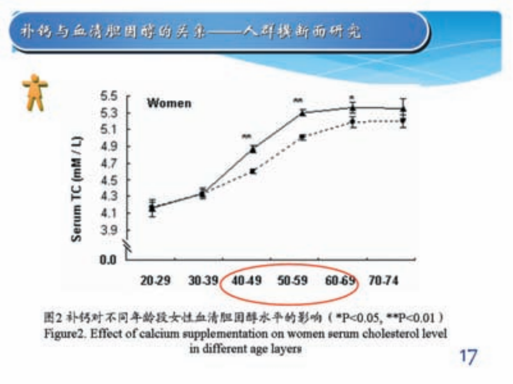
补钙与血清胆固醇的关系——人群横断面研究

图2 补钙对不同年龄段女性血清胆固醇水平的影响（*P<0.05, **P<0.01）
Figure2. Effect of calcium supplementation on women serum cholesterol level in different age layers

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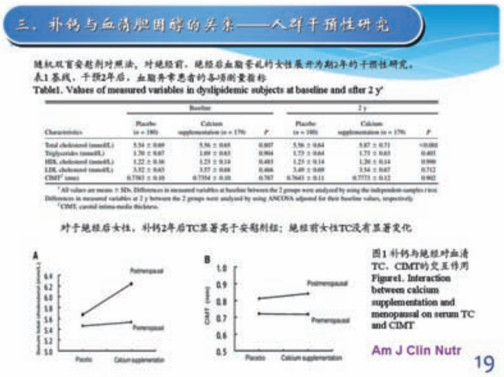
高钙
Ca
绝经前女性血脂水平
绝经后女性血脂水平



三、补钙与血清胆固醇的关系——人群干预性研究

随机双盲安慰剂对照法，对绝经前、绝经后血脂紊乱的女性展开为期2年的干预性研究。

表1 基线、干预2年后，血脂异常患者的各项测量指标

Table1. Values of measured variables in dyslipidemic subjects at baseline and after 2 y¹

Characteristics	Baseline Placebo (n = 180)	Baseline Calcium supplementation (n = 179)	Baseline P	2 y Placebo (n = 180)	2 y Calcium supplementation (n = 179)	2 y P
Total cholesterol (mmol/L)	5.54 ± 0.69	5.56 ± 0.65	0.807	5.56 ± 0.64	5.87 ± 0.71	<0.001
Triglycerides (mmol/L)	1.70 ± 0.67	1.69 ± 0.65	0.904	1.73 ± 0.64	1.71 ± 0.65	0.403
HDL cholesterol (mmol/L)	1.22 ± 0.16	1.23 ± 0.14	0.403	1.23 ± 0.14	1.20 ± 0.14	0.990
LDL cholesterol (mmol/L)	3.52 ± 0.65	3.57 ± 0.68	0.466	3.49 ± 0.69	3.54 ± 0.67	0.712
CIMT² (mm)	0.7583 ± 0.10	0.7354 ± 0.10	0.787	0.7643 ± 0.11	0.7773 ± 0.12	0.902

¹ All values are means ± SDs. Differences in measured variables at baseline between the 2 groups were analyzed by using the independent-samples t test. Differences in measured variables at 2 y between the 2 groups were analyzed by using ANCOVA adjusted for their baseline values, respectively.

² CIMT, carotid intima-media thickness.

对于绝经后女性，补钙2年后TC显著高于安慰剂组；绝经前女性TC没有显著变化

A
Serum total cholesterol (mmol/L)
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
Postmenopausal
Premenopausal
Placebo
Calcium supplementation
B
CIMT (mm)
1.0
0.9
0.8
0.7
0.6
0.5
Postmenopausal
Premenopausal
Placebo
Calcium supplementation

图1 补钙与绝经对血清TC、CIMT的交互作用
Figure1. Interaction between calcium supplementation and menopausal on serum TC and CIMT

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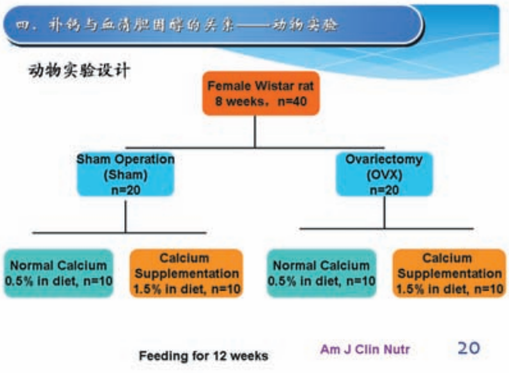

四、补钙与血清胆固醇的关系——动物实验

动物实验设计

Female Wistar rat
8 weeks，n=40

Sham Operation
(Sham)
n=20

Ovariectomy
(OVX)
n=20

Normal Calcium
0.5% in diet, n=10

Calcium
Supplementation
1.5% in diet, n=10

Normal Calcium
0.5% in diet, n=10

Calcium
Supplementation
1.5% in diet, n=10

Feeding for 12 weeks

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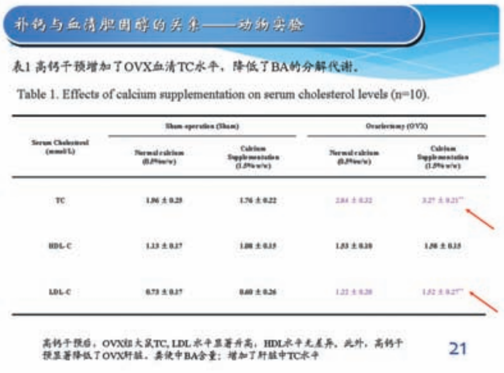


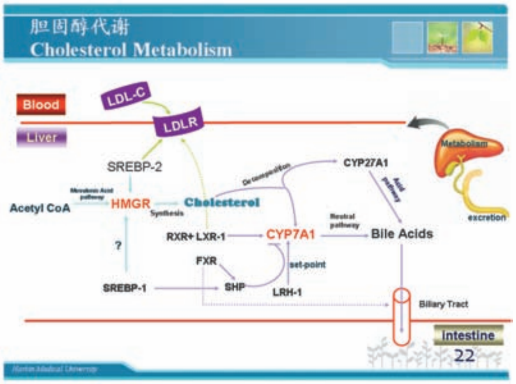
补钙与血清胆固醇的关系——动物实验

表1 高钙干预增加了OVX血清TC水平，降低了BA的分解代谢。

Table 1. Effects of calcium supplementation on serum cholesterol levels (n=10).

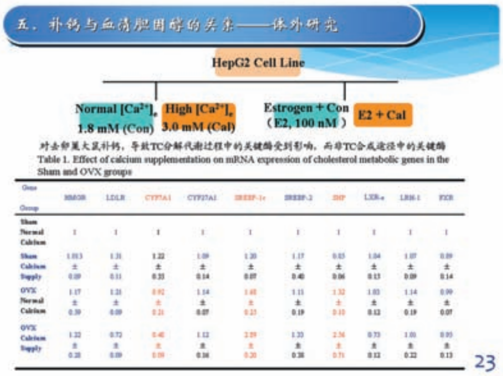
Serum Cholesterol (mmol/L)	Sham operation (Sham)		Ovariectomy (OVX)	
	Normal calcium (0.5%w/w)	Calcium Supplementation (1.5% w/w)	Normal calcium (0.5%w/w)	Calcium Supplementation (1.5% w/w)
TC	1.96 ± 0.25	1.76 ± 0.22	2.84 ± 0.32	3.27 ± 0.21**
HDL-C	1.13 ± 0.17	1.08 ± 0.15	1.03 ± 0.10	1.08 ± 0.15
LDL-C	0.73 ± 0.17	0.60 ± 0.26	1.22 ± 0.20	1.52 ± 0.27**

高钙干预后，OVX组大鼠TC, LDL水平显著升高，HDL水平无差异。此外，高钙干预显著降低了OVX肝脏、粪便中BA含量；增加了肝脏中TC水平



胆固醇代谢
Cholesterol Metabolism

Blood
LDL-C
LDLR
Liver
Metabolism
SREBP-2
Mevalonic Acid pathway
Decomposition
CYP27A1
Acid pathway
Acetyl CoA
HMGR
Synthesis
Cholesterol
excretion
Neutral pathway
RXR+ LXR-1
CYP7A1
Bile Acids
?
FXR
set-point
SREBP-1
SHP
LRH-1
Biliary Tract
Intestine
Harbin Medical University



五、补钙与血清胆固醇的关系——体外研究

HepG2 Cell Line

Normal [Ca²⁺]ₑ 1.8 mM (Con)

High [Ca²⁺]ₑ 3.0 mM (Cal)

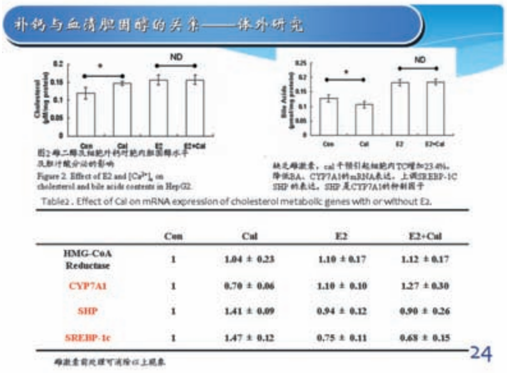
Estrogen + Con（E2, 100 nM）

E2 + Cal

对去卵巢大鼠补钙，导致TC分解代谢过程中的关键酶受到影响，而非TC合成途径中的关键酶

Table 1. Effect of calcium supplementation on mRNA expression of cholesterol metabolic genes in the Sham and OVX groups

Gene / Group	HMGR	LDLR	CYP7A1	CYP27A1	SREBP-1c	SREBP-2	SHP	LXR-α	LRH-1	FXR
Sham Normal Calcium	1	1	1	1	1	1	1	1	1	1
Sham Calcium Supply	1.013 ± 0.09	1.31 ± 0.11	1.22 ± 0.33	1.09 ± 0.14	1.20 ± 0.07	1.17 ± 0.40	0.85 ± 0.06	1.04 ± 0.13	1.07 ± 0.09	0.89 ± 0.14
OVX Normal Calcium	1.17 ± 0.39	1.21 ± 0.09	0.92 ± 0.21	1.14 ± 0.07	1.48 ± 0.23	1.11 ± 0.19	1.32 ± 0.10	1.03 ± 0.12	1.14 ± 0.19	0.99 ± 0.07
OVX Calcium Supply	1.22 ± 0.28	0.72 ± 0.09	0.40 ± 0.09	1.12 ± 0.16	2.19 ± 0.20	1.33 ± 0.38	2.34 ± 0.71	0.73 ± 0.12	1.01 ± 0.22	0.93 ± 0.13



补钙与血清胆固醇的关系——体外研究

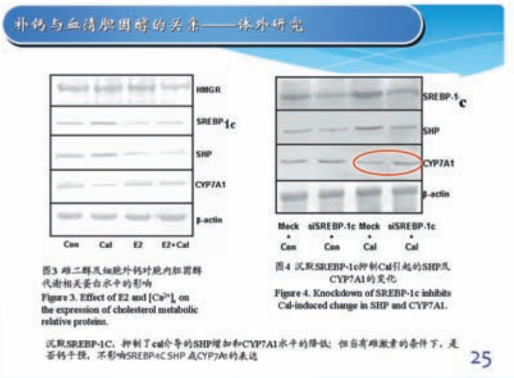
图2 雌二醇及细胞外钙对胞内胆固醇水平及胆汁酸分泌的影响
Figure 2. Effect of E2 and [Ca²⁺]ₑ on cholesterol and bile acids contents in HepG2.

缺乏雌激素，cal干预引起细胞内TC增加23.4%，降低BA、CYP7A1的mRNA表达，上调SREBP-1C SHP的表达。SHP是CYP7A1的抑制因子

Table2. Effect of Cal on mRNA expression of cholesterol metabolic genes with or without E2.

	Con	Cal	E2	E2+Cal
HMG-CoA Reductase	1	1.04 ± 0.23	1.10 ± 0.17	1.12 ± 0.17
CYP7A1	1	0.70 ± 0.06	1.10 ± 0.10	1.27 ± 0.30
SHP	1	1.41 ± 0.09	0.94 ± 0.12	0.90 ± 0.26
SREBP-1c	1	1.47 ± 0.12	0.75 ± 0.11	0.68 ± 0.15

雌激素前处理可消除以上现象



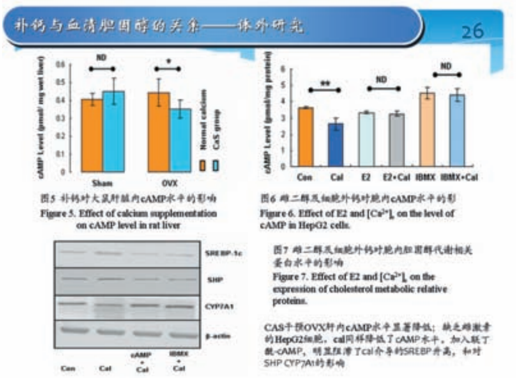
补钙与血清胆固醇的关系——体外研究

HMGR
SREBP 1c
SHP
CYP7A1
β-actin
Con
Cal
E2
E2+Cal
SREBP-1c
SHP
CYP7A1
β-actin
Mock + Con
siSREBP-1c + Con
Mock + Cal
siSREBP-1c + Cal

图3 雌二醇及细胞外钙对胞内胆固醇代谢相关蛋白水平的影响
Figure 3. Effect of E2 and [Ca²⁺]ₑ on the expression of cholesterol metabolic relative proteins.

图4 沉默SREBP-1c抑制Cal引起的SHP及CYP7A1的变化
Figure 4. Knockdown of SREBP-1c inhibits Cal-induced change in SHP and CYP7A1.

沉默SREBP-1C，抑制了cal介导的SHP增加和CYP7A1水平的降低；但当有雌激素的条件下，是否钙干预，不影响SREBP-1C SHP 或CYP7A1的表达



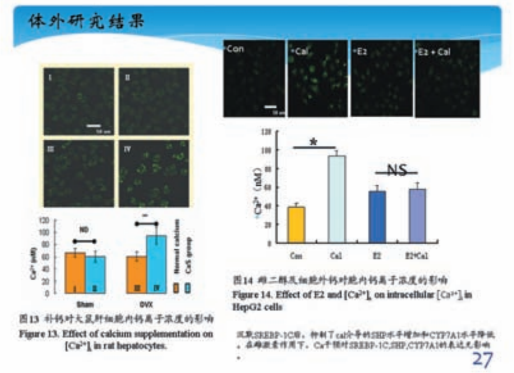
补钙与血清胆固醇的关系——体外研究

图5 补钙对大鼠肝脏内cAMP水平的影响
Figure 5. Effect of calcium supplementation on cAMP level in rat liver

图6 雌二醇及细胞外钙对胞内cAMP水平的影
Figure 6. Effect of E2 and $[Ca^{2+}]_o$ on the level of cAMP in HepG2 cells.

图7 雌二醇及细胞外钙对胞内胆固醇代谢相关蛋白水平的影响
Figure 7. Effect of E2 and $[Ca^{2+}]_o$ on the expression of cholesterol metabolic relative proteins.

CAS干预OVX肝内cAMP水平显著降低；缺乏雌激素的HepG2细胞，cal同样降低了cAMP水平，加入联丁酰-cAMP，明显阻滞了cal介导的SREBP升高，和对SHP CYP7A1的影响

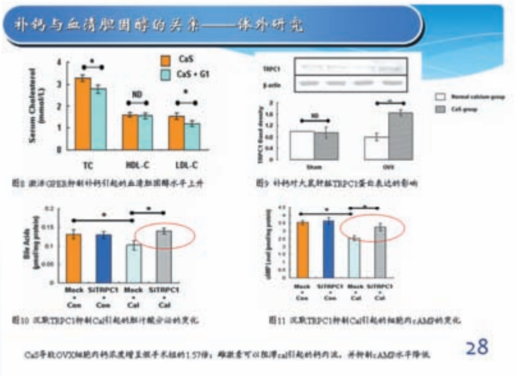


体外研究结果

图13 补钙对大鼠肝细胞内钙离子浓度的影响
Figure 13. Effect of calcium supplementation on $[Ca^{2+}]_i$ in rat hepatocytes.

图14 雌二醇及细胞外钙对胞内钙离子浓度的影响
Figure 14. Effect of E2 and $[Ca^{2+}]_o$ on intracellular $[Ca^{2+}]_i$ in HepG2 cells

沉默SREBP-1C后，抑制了cal介导的SHP水平增加和CYP7A1水平降低，在雌激素作用下，Ca干预对SREBP-1C,SHP,CYP7A1的表达无影响。



补钙与血清胆固醇的关系——体外研究

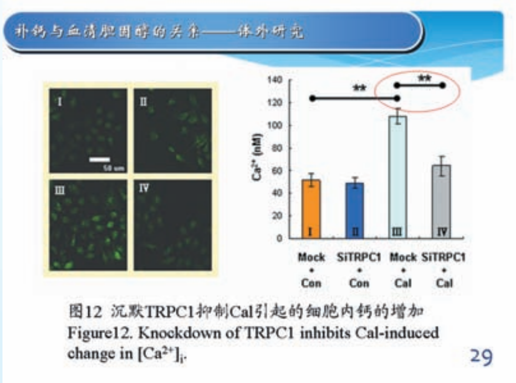
图8 激活GPER抑制补钙引起的血清胆固醇水平上升

图9 补钙对大鼠肝脏TRPC1蛋白表达的影响

图10 沉默TRPC1抑制Cal引起的胆汁酸分泌的变化

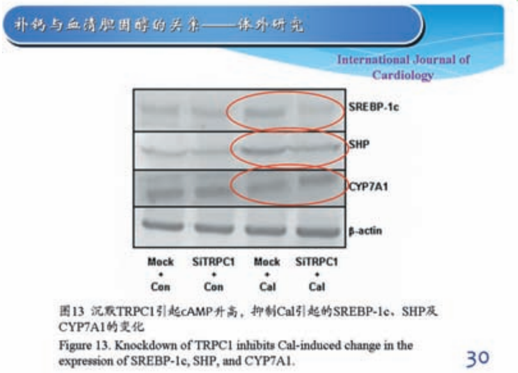
图11 沉默TRPC1抑制Cal引起的细胞内cAMP的变化

CaS导致OVX细胞内钙浓度增至假手术组的1.57倍；雌激素可以阻滞cal引起的钙内流，并抑制cAMP水平降低



补钙与血清胆固醇的关系——体外研究

图12 沉默TRPC1抑制Cal引起的细胞内钙的增加
Figure12. Knockdown of TRPC1 inhibits Cal-induced change in $[Ca^{2+}]_i$.

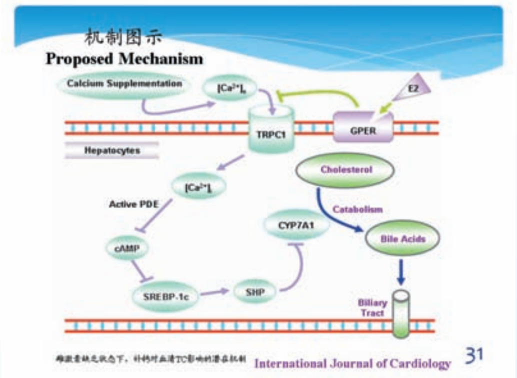


补钙与血清胆固醇的关系——体外研究

International Journal of Cardiology

SREBP-1c
SHP
CYP7A1
β-actin
Mock + Con
SiTRPC1 + Con
Mock + Cal
SiTRPC1 + Cal

图13 沉默TRPC1引起cAMP升高，抑制Cal引起的SREBP-1c、SHP及CYP7A1的变化
Figure 13. Knockdown of TRPC1 inhibits Cal-induced change in the expression of SREBP-1c, SHP, and CYP7A1.

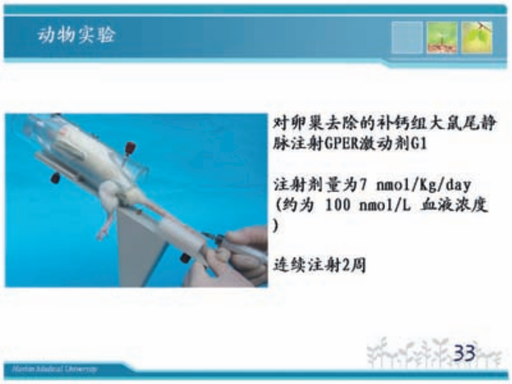


机制图示
Proposed Mechanism

Calcium Supplementation
$[Ca^{2+}]_o$
E2
TRPC1
GPER
Hepatocytes
Cholesterol
$[Ca^{2+}]_i$
Active PDE
Catabolism
CYP7A1
Bile Acids
cAMP
SREBP-1c
SHP
Biliary Tract

雌激素缺乏状态下，补钙对血清TC影响的潜在机制

International Journal of Cardiology

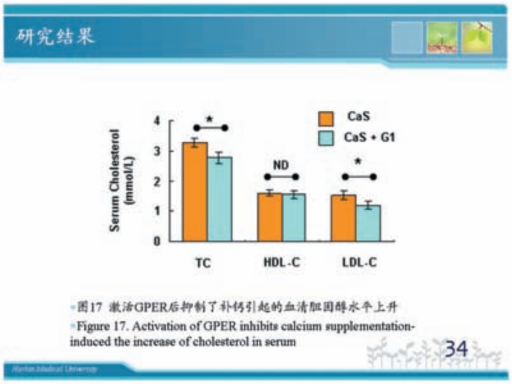


动物实验

对卵巢去除的补钙组大鼠尾静脉注射GPER激动剂G1

注射剂量为7 nmol/Kg/day（约为 100 nmol/L 血液浓度）

连续注射2周



研究结果

图17 激活GPER后抑制了补钙引起的血清胆固醇水平上升
Figure 17. Activation of GPER inhibits calcium supplementation-induced the increase of cholesterol in serum

学术意义

1. 明确低钙膳食对肥胖的作用
2. 阐明了作用机制
3. 明确了补钙对血清总胆固醇的作用
4. 阐明作用机制
5. 我国居民由于其膳食结构特点决定其为低钙膳食群体，通过大规模人群研究，探讨钙摄入与疾病的关系，为制定我国居民的膳食参考摄入量提出建议和提供科学依据。

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Thank you!