| **Table 1.** Summary of the human and animal studies reviewed | | | | | | |
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| **Author, Year** | **Animals/ Subjects** | **Intervention** | **Type/ Source of Ca** | **Dose of Ca** | **Period** | **Main outcomes** |
| Govers & Meer (1993)40 | 6 female Wistar rats/ group | 1)Control diet  2, 3 and 4): Low/high Ca diet associated with low/ high phosphate | CaCO3 | 25, 75, or 225 µmol Ca /g diet;  75, 125, 275 µmol phosphate /g diet. | 2 weeks | High-Ca diet (independent of the phosphate content): ↓ cytotoxicity of FW. ↑ fecal excretion of FA. ↓ [BA] and [↓ FA] in the FW. Ca did not change solubility of BA in the ileum, but ↓ 20% solubility of BA in the colon and feces. ↓ solubility of FA in the ileum, colon, and feces. |
| Lapré et al. (1993)36 | 6 male Wistar rats/ group | 1) Control diet (low-Ca diet);  2, 3 and 4) High-Ca diet associated with: butter, saturated margarine, and polyunsaturated margarine | CaHPO4. | 25 or 225 µmol Ca/g diet | 2 weeks | High-Ca diets: ↓ cytotoxicity of FW, mainly in PUFA-diet. ↑ fecal excretion of BA and FA. ↓[BA] and ↓ [FA] in the LFW. No changes in the fecal pH. |
| Govers et al. (1994)37 | 7 male Wistar rats/ group | 1) Control diet (Low-Ca diet);  2) Dairy Ca;  3) Carbonate Ca;  4) CaP. | Milk Ca; CaCO3;  CaHPO4 | 30 mmol/ kg (control diet) or 150 mmol/kg diet. | 2 weeks | All high-Ca diets: ↓ cytotoxicity of FW. ↓ [BA] and↓ [FA] in the FW. ↓ fecal pH. ↓ cellular damage and epithelium proliferation. ↑ [serum gastrin]. |
| Bovee et al. (1996)26 | 9 pathogen free male Wistar rats/ group | 1) Low Ca milk; 2) Milk; 3) Acidified milk; 4)Yoghurt  Infection with *Salmonella enteritidis* | Milk, acidified milk and yoghurt | 6 or 30 mmol Ca/l | 12 days | All high-Ca diets: ↓ cytotoxicity of FW. ↓ [BA] in the FW. |
| Govers et al. (1996)41 | 13 healthy males (mean age 38 + 2 y) | 1) Control diet (Low-Ca diet).  2) High-Ca diets (Milk and/or yogurt 3% fat, 1 liter/ day, according to personal preference) | Milk and/or yogurt | 120 or 1200 Ca mg/day | 1 week | All high-Ca diets: ↓ cytotoxicity of FW in 11 of 13 subjects. ↓ [BA] (mainly secondary BA), ↓ [FA] (cytotoxic FA C16-C18 and cholesterol), and [phosphate] in the FW. ↑ fecal pH. |
| Bovee et al. (1997)27 | 9 males Wistar rats/ group | 1) Low-, 2)Medium-, or 3) High-Ca diet.  Infection with *Salmonella enteritidis*  ( after an adaptation period of 11 days) | CaHPO4  . 2H2O | 20, 60, or 180 mmol Ca/kg diet | 2 weeks | Medium and High-Ca diet:↓ cytotoxicity of FW. ↓ [BA] in the FW.↓ bacterial translocation. No changes in [FA] in the FW. |
| Bovee et al., (1999)38 | 8 male Wi rats/ group | 1) Control diet (Low-Ca diet);  2) High-Ca diet. | CaHPO4 . 2H2O | 20 or 180 mmol Ca/ kg diet | 6 days of dietary interven-tion after infection | High-Ca diet: ↓ cytotoxicity of FW. ↓ [FA] and ↓ [BA] in the ileum and in the FW (mainly secondary BA). ↓ diarrhea. ↓ bacterial translocation. ↑ lactobacilli in the ileum and feces before infection) (measured by colony-forming units/g feces). |
| Ten Bruggencate et al. (2004)50 | 8 male rats Wistar/ group | 1) Control diet (Low-Ca Low-inulin and Low-FOS-diet);  2) Low-Ca High-inulin diet;  3) High-Ca High-inulin diet ;  4) Low-Ca High-FOS diet;  5) High-Ca High-FOS diet.  Infection with *Salmonella enteritidis* | CaHPO4.2H2O | 30 ( control and low-Ca diets) or 100 mmol Ca/kg diet | 6 days | Low-Ca High-inulin and High-FOS diets: ↑ ↓ cytotoxicity of FW and ↑ bacterial translocation after inulin/FOS supplementation – these effects were decreased by high-Ca diets.  Low-Ca/ High-inulin and FOS- diets: ↓ fecal pH. ↑ fecal lactobacilli and enterobacteria.  High-Ca/High-inulin diet: ↑ fecal lactobacilli  High-Ca diets: ↓ fecal enterobacteria (measured by RT-PCR) and ↑ fecal lactate. |
| Ditscheid et al. (2009)42 | 31 healthy volunteers | 1) Placebo (without additional Ca);  2) High Ca-diet.  Double-blind, randomized cross-over trial. | Ca5(PO4)3OH | 1 g Ca/day | 4 weeks | High-Ca diet: ↑ fecal excretion of FA. No changes in fecal excretion of BA. ↓ [cholesterol, coprostanol, coprostanone and cholestanol] in the FW. |
| Rao (2009)81 | 6 male albino rats/ group | 1) Low-Ca diet ;  2) High-Ca diet. | Ca carbonate | 0.2% or 1.5% Ca | 21 days | High-Ca diet: ↑ passive transport of mannitol and Ca and ↓ active transport of Ca by the everted gut sacs. |
| Schepens et al. (2009)51 | HLA-B27 transgenic rats (n = 9 in control group diet and n=8 in high-Ca group) | 1) Low-Ca diet  2) High-Ca diet. | CaHPO4 | 30 or 120 mmol Ca/kg | 7 weeks | High-Ca diet: ↓ cytotoxicity of FW. ↓ [BA] in the FW in week 2 (this effect was not significant in week 6). ↓ diarrhea. ↓ IP (Cr-EDTA). ↓ antibodies against LPS (compared with control diet). ↑ mucosal barrier genes. |
| Metzler -Zebeli et al. (2010)57 | 8 growing pigs/ group | 1) Control diet (soybean) without pectin infusion;  2) Control diet (soybean) with pectin infusion;  3) High-CaP diet without pectin infusion;  4) High-CaP diet with pectin infusion. | Monocalcium  phosphate | 3 g of phosphate/kg diet (control diets) or  15 g Ca/kg diet | 22 days | High Ca-diets: No changes in lactobacilli and total bacteria. ↓ *Enterococcus spp*., *E. faecium* and *C. leptum* in the ileum (measured by RT-PCR). ↑ acetate in the ileum. No changes for Other SCFA (ileum and feces). |
| Schepens et al. (2010)67 | 13 male Wistar rats/group | 1 ) Control (low-Ca and FOS diet);  2) High-Ca diet;  3) High-FOS diet. | CaHPO4.2H2O | 30 or 120mmol Ca/kg diet | 14 days | High Ca-diet: ↑ fecal pH. ↓ enterobacteria fecal (colony-forming units/g faeces).↓ IP (↓ Cr-EDTA excretion, ↑ lactulose: mannitol ratio, no changes in lactulose excretion. |
| Van Ampting et al. (2010)52 | 8 male Wistar rats/ group  (Control diet1, n=5) | 1) Control diet1: diet without antibiotic and without infection;  2) Control diet 2: diet without antibiotic and with  *Salmonella enteritidis* infection;  3) Control diet 3: diet with antibiotic and with infection;  4) High-Ca diet with antibiotic and with infection;  5) High tannic acid diet with antibiotic and with infection. | CaHPO4.2H2O | 1.2 or 4.8g/kg or diet | 8 days | High-Ca diet: ↓ cytotoxicity of FW. ↓ diarrhea. No change in bacterial translocation. ↑ fecal lactobacilli (log CFU/g feces). ↓ IP (Cr-EDTA excretion). ↓ anti-LPS antibodies. |
| Metzler -Zebeli et al. (2011)58 | 8 weaned pigs/ group | 1) Control diet (cornstarch casein based diet – low Ca and phosphate);  2) High-CaP diet  3) High-CaP diet + β-glucan ;  4) Low-CaP diet + β-glucan. | Dicalcium phosphate | 5.4g or 10g Ca/kg diet | 14 days | No changes in gastric, cecal and colonic pHs.  High Ca-diets:↓ gastric streptococci. No changes in lactobacilli (bacterial 16S rRNA genes quantified by qPCR). ↓ gastric lactate and propionate in the large intestine. |
| Ten Bruggencate et al. (2011)56 | 8 male Wistar rats/ group | 1) Low Ca-diet;  2, 3, 4 and 5) High-Ca diets: CaP; milk Ca; Ca chloride; Ca carbonate  Infection with *S. enteritidis* 2 weeks after adaptation.  High-fat, Western human-style, purified diet. | CaHPO4,  milk Ca (29% Ca), Ca carbonate or Ca chloride | 20 or 100 mmol Ca/kg diet | 7 days of dietary intervention after infection | No changes in lactobacilli.  High CaP and milk Ca: ↓ enterobacteria  All high-Ca diets: ↓ PI induced by *Salmonella.* |
| Schepens et al. (2011)80 | HLA-B27 transgenic rats (n=9/ group) nontransgenic  counterparts (n=7) | 1 ) Control (low Ca and glutathione, Vit C and Vit. E;  2) Low Ca + High glutathione, Vit C and Vit. E ;  3) High Ca + glutathione, Vit C and Vit. E. | CaHPO4.2H2O | 30 ( control and low-Ca diets) or 120mmol Ca/kg diet | 9 weeks | High Ca-diet: ↓ IP (Cr-EDTA). ↓ diarrhea. |
| Schepens et al. (2012)47 | 10 male Wistar rats | 1) FOS + Low-Ca diet + medium phosphate;  2, 3 and 4) FOS + High-Ca diet associated with low-, medium- or high- phosphate. | CaHPO4.2H2O | 30 mmol or 120 mmolCa/kg  35, 70 or 160 mmol phosphate/kg diet. | 20 days | High-Ca medium-phosphate diet and High-Ca High- phosphate diet x High-Ca Low- phosphate diet and Low-Ca Low- phosphate diet: ↓ IP (Cr-EDTA excretion).  High-Ca diets: prevented the FOS-induced increase in the IP. ↓ cytotoxicity of FW. ↓ cecal lactate.  High-Ca High- phosphate diet x Low-Ca Low- phosphate diet : ↑cecal pH. |
| Trautvetter et al. (2012)43 | 32 healthy men and women (aged 25+5 y and BMI of 22+3 kg/m2) | 1) Lactobacilli;  2) Lactobacilli + High-CaP;  3) Placebo.  Double-blind, placebo-controlled, cross-over trial. | Pentacalcium  hydroxy-triphosphate (Ca5(PO4)3OH) | 1g/day | 4 weeks (washout: 2 weeks) | High-CaP diet x Control diet and Lactobacilli-diet: ↑ secondary BA fecal excretion. No changes in fecal excretion of FA.  Control diet and High-Ca diet: ↑ fecal pH.  High-CaP and Lactobacilli-diet (*vs.* placebo): ↑ fecal lactobacilli (qRT-PCR)  High-CaP diet: ↓ cholesterol total and LDL-c |
| Hwang et al. (2013)88 | 5 mice per group:  1) wild-type  2) Calb-9k KO  3) Calb-28k KO  3) Calb-9k/28k KO | 1) Normal diet (AIN-76A,)  2) Ca-deficient diet (AIN-76A, 1% phosphate);  3) Ca/ vit D-deficient diet (AIN-76A, 0.35% phosphate) | Ca carbonate anhydrous | 1.1% Ca (normal diet) or 0.02% (Ca-deficient diet). | 4 weeks | Normal diet: ↑ expression of tight junctions genes in calbindin-9k KO mice *vs.* wild-type ones.  Calbindin-9K KO mice fed Ca-Vit. D -deficient diet *vs*. normal diet: ↓occludin, ZO*-1*, claudin 2 and 15*.* |
| Metzler-Zebeli et al. (2013)59 | 8 weaned pigs/ group | 1) Wheat-barley diet with adequate CaP content;  2) Wheat-barley diet with high CaP content;  3) Corn diet with adequate CaP content ;  4) Corn diet with high CaP content | Monocalcium phosphate | 8.2 or 14.8 g Ca/kg diet. | 14 days | No changes in gastric, ileal, colonic, and fecal pHs. No changes in serum LPS and fecal LPS.  High-CaP diets: ↑ gastric *Enterobacteriaceae* and ileal *Enterococcus*, *Bacteroides-Prevotella-Porphyromonas*, and *Campylobacter*. ↓ caproate in the colon (qPCR).  High CaP level increased total SCFA, acetate, and isovalerate in gastric digesta, when combined with the wheat-barley diet but not with the corn diet. |
| Overduin et al. (2013)70 | 7 or 8 pathogen-free Wistar rats/ group | 1) Low-Ca low-GOS diet;  2) High-Ca low-GOS diet;  3) Low-Ca high -GOS diet;  4) High-Ca high-GOS diet. | Ca monophosphate | 30 or 100 Ca mmol/kg diet;  0 or 6% GOS of dry weight. | 3 weeks | High-GOS diets:↑ lactic acid levels and ↓ butyric acid in proximal colonic contents;  High-Ca diets: abolished the GOS-related elevation of lactic acid, while increasing propionic acid levels. |
| Trautvetter et al. (2014)8 | 10 healthy men  (aged 27 + 4y and mean BMI of 23.1 + 2.3 kg/m2) | 1) Placebo;  2) High-CaP diet.  Double-blind, placebo-controlled, cross-over trial. | Ca5(PO4)3OH | 1 g/day | 3 weeks (washout: 2 weeks) | ↑ AUC of GLP-1 (total and active) and GLP-2 after the repeated CaP administrations x placebo.  No changes in insulin and glucose. |
| Metzeler-Zebeli et al. (2015)91 | 8 weaned pigs/ group | 1) Wheat-barley diet with adequate CaP content;  2) Wheat-barley diet with high CaP content;  3) Maize diet with adequate CaP content ;  4) Maize diet with high CaP content. | Monocalcium phosphate | 8.2 or 14.8 g Ca/kg diet. | 15 days | High-Ca diets *vs.* adequate Ca diets: ↓ jejunal ZO-1and occludin expression. |
| Zheng et al. (2015)44 | 15 healthy young men (ages, 18−50 years; BMI 20−28 kg/m2) | 1) Control diet;  2) High in semiskimmed milk;  3) High in semihard cow’s cheese with equal amounts of dairy calcium. | Dairy Ca | 0 (control diet) or 1.7 g/day. | 14 days | Cheese and milk consumption: ↑ fecal excretion of acetate, propionate, and lipid;  Cheese *vs.* milk consumption: ↑butyrate,  hippurate, and malonate. |

AUC, area under the curve; BA, bile acid; BMI, body mass index; Ca, calcium; Calb, calbindin; CaP, calcium phosphate; FA, fatty acid; FOS, fructooligosaccharides; FW, fecal water; GLP-1, glucagon-like peptide-1; GLP-2, glucagon-like peptide-2; GOS, galacto-oligosaccharides; IP, intestinal permeability; KO, Knouckout; LDL-c, Low-density lipoprotein- cholesterol; LPS, lipopolysaccharide; PUFA, polyunsaturated fatty acids; qPCR, quantitative PCR;

qPCR, quantitative polymerase chain reaction; RT-PCR, Real-time polymerase chain reaction; SCFA, short-chain fatty acids; Vit., vitamin; ZO-1, zonula occludens 1; ↓, decrease; ↑, increase; [ ], concentration