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## RESEARCH ARTICLE

# OBESITY AND INFLAMMATION. PROBIOTICS OR PHARMACEUTICALS INTERVENTION?

M.R. Graham<sup>1\*</sup>, B. Davies<sup>2</sup>, Pates J<sup>3</sup>, P.J. Evans<sup>4</sup> and J.S. Baker<sup>5</sup>

<sup>1</sup>MBChB, PhD, Llantarnam Research Academy, Newport Road, Llantarnam, Cwmbran, UK

<sup>2</sup>FACSM, Health and Exercise Science Department, University of South Wales, UK

<sup>3</sup>Bournville College, Birmingham, UK

<sup>4</sup>Royal Gwent Hospital, Newport, Wales, UK

<sup>5</sup>FRSM, FHBA, FSB, FICR, C.Biol, C.Sci Director of Research, Institute of Clinical Exercise and Health Science, Applied Physiology Research Laboratory, School of Science and Sport, University of the West of Scotland, Hamilton, Lanarkshire, Scotland

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### ABSTRACT

Epidemiological studies of anti-obesity medicines depict short-term success, but long-term contraindications. The pharmaceutical industry demonstrates an exponential increase in withdrawn medicines.

History has demonstrated retrospectively that prescription medicines have cost countless lives and billions of dollars in compensation.

Currently the pharmaceutical industry only appears to be able to palliate the problem in its provision of medicines to balance the energy metabolism equations which control weight. New medicines and lower doses of older failed medications to combat the obesity pandemic are being researched, but should we not look to our own gastrointestinal microbiota and probiotic bacteria ("probiotics") to provide an answer? Probiotics are live microorganisms which when ingested in adequate quantities, confer health benefits on the host. The identification that the dietary ingestion of specific bacteria that can decrease the inflammatory responses of ageing, may have a dramatic influence on the management of obesity, without the side effects of traditional pharmacotherapies.

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## INTRODUCTION

### Managing the Obesity Epidemic

The obesity epidemic that we are experiencing is a global phenomenon. A survey of 188 countries shows that nearly 30 percent of the global population, or 2.1 billion people, are either overweight or obese (<http://www.nbcnews.com/health/diet-fitness/whole-world-getting-fatter-new-survey-finds-n115811>).

The mechanisms associated with being overweight or obese have been used by the pharmaceutical industry to identify specific targets in an attempt to design pharmaceutical agents that can control body weight.

Anti-obesity medicines act by suppressing appetite (anorectics) and decreasing energy intake, increasing energy expenditure or controlling lipid metabolism and fat stores.

Despite the escalation in obesity over the last half century and our pre-occupation with our images, there are remarkably few medicines available which are effective in managing the problem. Since the 1950s, various medications have been approved only to be withdrawn later, because of adverse health issues.

In the UK the treatment of National Health Service (NHS) patients currently extends to the prescription of oral anti-obesity pharmacological medication, the offer of calorie controlled diet sheets, referral to local weight loss groups and possible referral for exercise prescription.

The National Institute for Health and Care Excellence (NICE) in the UK, stipulate that prescription medicines can only be prescribed if the risks associated with obesity outweigh the risks of treatment (<http://www.nice.org.uk/guidance/cg189/chapter/introduction#medicines-recommendations>). Weight loss drugs approved by NICE and by the Food and Drug Administration (FDA) in the USA, may only be used as part of a comprehensive weight loss

\*Corresponding author: M.R. Graham

MBChB, PhD, Llantarnam Research Academy, Newport Road, Llantarnam, Cwmbran, UK

program. This should include dietary therapy and physical activity, for patients with a body mass index (BMI) of 30 kg/m<sup>2</sup>, with no concomitant obesity-related risk factors and for patients with a BMI of 28 kg/m<sup>2</sup>, with one or more concomitant obesity-related risk factors. The risk factors and diseases considered important enough to warrant pharmacotherapy at a BMI of 28-29.9 kg/m<sup>2</sup>, are hypertension, dyslipidaemia, coronary heart disease (CHD), type 2 diabetes, and sleep apnoea (National Institutes of Health, National Heart, Lung, and Blood Institute, 1998). The aetiology of obesity is complex and a combination of genetic, environmental, and psychological factors. We are led to believe that obesity is a disorder of energy balance. When energy derived from food, chronically exceeds energy expenditure, the excess calories are stored as triglycerides in adipose tissue. Despite the marked fluctuations in daily food intake, body weight remains remarkably stable in most humans. In response to alterations in body adiposity, the brain triggers compensatory physiological adaptations that resist weight change. The causation of obesity has been suggested as being an unhealthy diet, excessive calorie intake over expenditure and a sedentary lifestyle.

Numerous scientific studies within this and the latter part of the last century have been conducted in an attempt to identify the reasons for the increase.

Geneticists have identified genes such as the obesity gene (FTO) (Frayling *et al*, 2007), a low fat gene (APOA5) (Corella *et al*, 2007), and that variations in the adiponectin gene (SNP 276 G Allele) can lead to hypoadiponectinaemia, which then results in insulin resistance, the metabolic syndrome, increased atherosclerosis and ultimately premature morbidity and mortality. Using exome sequencing a low-frequency coding variant in the SYPL2 gene that was associated with morbid obesity has been identified (Jiao *et al*, 2014).

There is an assumption that genetics, whether they are single or multiple nucleotide mutations could be responsible for polymorphisms resulting in this obesity epidemic. Geneticists are attempting to identify a specific genetic code which produces a variant lipid polymorphism which causes increased adiposity. In the interim we have been relying on the pharmaceutical industry to control the obesity epidemic which has befallen such a large percentage of the global population.

Currently the pharmaceutical industry only appears to be able to palliate the problem in its provision of medicines to balance the energy metabolism equations which control weight.

### **The Advent of Probiotics**

Could probiotic bacteria ("probiotics") provide an answer? Probiotics are live microorganisms which when ingested in adequate quantities, confer health benefits on the host. The identification that the dietary ingestion of a specific bacterium that can decrease the inflammatory responses of ageing, may have a dramatic influence on the management of obesity, without the side effects of traditional pharmacotherapies (Poutahidis *et al*, 2014). In this study, indicators which are typical of senescence were restored to youthful levels, by ingestion of probiotics, comparable to using systemic administration of antibodies blocking pro-

inflammatory cytokines, such as interleukin-17A. Interleukin 17 is a cytokine that acts as a potent mediator in delayed-type reactions by increasing chemokine production in various tissues to recruit monocytes and neutrophils to the site of inflammation, similar to interferon gamma (IFN- $\gamma$ ). Interleukin 17 as a family, functions as a pro-inflammatory cytokine that responds to the invasion of the immune system by extracellular pathogens and induces destruction of the pathogen's cellular matrix. There is a correlation between probiotic consumption and IL-10 and IL-17 secreted by peripheral blood mononuclear cells in overweight and obese people (Zarrati *et al*, 2013). The intestinal microorganisms or bacteria (microbiota) play a fundamental role in maintaining immune homeostasis (Ng *et al*, 2009). Probiotics can influence the immune system by their metabolites, cell wall components and deoxyribonucleic acid (DNA). Products of probiotics are recognised by host cells with pattern recognition receptors (Oelschlaeger *et al*, 2010). Experimental studies have demonstrated the lipid-lowering effects of certain bacterial strains, such as Bifidobacterium species in high fat diet-induced obese rats (An *et al*, 2011). Is it possible that our future health relies on understanding our symbiosis with dietary probiotics or should we continue in the pursuit of pharmaceuticals, which do not appear to be having the desired effect?

The human gastrointestinal tract (GIT) is sterile at birth, but is immediately colonised by thousands of species of microbiota from both maternal and environmental provenance. The human microbiota contains as many as 10<sup>14</sup> bacterial cells, an enormous microbial ecosystem. This is ten times the number of host body tissue cells of which the colon is estimated to contain over 70% of all the microbes in the human body (Ley *et al*, 2006). Metagenomic analysis of the human GIT microbiota has discovered more than 3.3 million genes, compared to the circa 23,000 genes present in the cells of the entire human host. There is increased evidence that the GIT microbiota is responsible for homeostasis of human health and chronic disease prevention, such as inflammatory conditions, which can then lead to autoimmune diseases, obesity, type 2 diabetes mellitus, cardiovascular disease and cancer, to name but a few (Carvalho *et al*, 2013). Microbiota imbalance (dysbiosis) in the GIT is associated with varied inflammatory disease processes. The majority of bacterial phyla in the human GIT includes Bacteroidetes, Firmicutes, and Actinobacteria (Neish, 2009).

Almost all bacteria present in the distal GIT and faeces belong to the phyla Bacteroidetes and Firmicutes (Gill *et al*, 2006).

Comparisons of the distal GIT microbiota of genetically obese mice and their lean littermates, as well as those of obese and lean human volunteers have revealed that obesity is associated with changes in the relative abundance of the two dominant bacterial divisions, the Bacteroidetes and the Firmicutes. In genetically obese (*ob/ob*) mice, there is an increased prevalence of Firmicutes bacteria and a corresponding decrease of Bacteroidetes, suggesting that this microbiota difference is associated with this type of metabolism (Ley *et al*, 2005). Germ-free mice that were infected with the GIT microbiota content of conventionally raised mice displayed insulin resistance and glucose intolerance within 14 days and a 60% increase in body fat content, even with a reduction in standard

food intake (Bäckhed *et al*,2004). A lipoprotein lipase (LPL) inhibitor, fasting-induced adipocyte factor (Fiaf) or angiopoietin-like protein 4 (ANGPTL4), controlled the fat storage in the conventionalised *germ-free* mice. The GIT microbiota induced selective suppression of the protein Fiaf (ANGPTL4) in intestinal cells and promoted an increase in LPL activity. This resulted in increased triglyceride storage in adipocytes, which was prevented upon the conventionalisation of Fiaf<sup>-/-</sup> *germ-free* mice (Bäckhed *et al*,2004).

Fiaf(ANGPTL4) inhibits lipoprotein lipase and is associated with dyslipidaemia. The expression of ANGPTL4 is regulated by free fatty acids (FFA) that activate lipid-sensing peroxisome proliferator-activated receptors (PPARs), but FFA can also activate pattern recognition receptors including “toll-like” receptor 4 (TLR4) protein in macrophages (Tjeerdema *et al*,2014).

Subsequent microbiota infection from *ob/ob* mice to *germ-free* mice resulted in a significant increase in body fat content when compared with *germ-free* mice that received lean mice microbiota, suggesting that the microbiota induced the obese phenotype (Turnbaugh *et al*,2006). Similarly the microbiota in the faeces of lean and obese humans differs, comparable to mice (Turnbaugh *et al*,2006). The difference in microbiota from *ob/ob* genetically obese mice would appear to be the ability to produce the enzymes capable of synthesising more energy from the dietary nutrients (Ferraris and Vinnakota, 1995).

There appears to be a balance in favour of an increased prevalence of *Firmicutes* phylum and a reduction in *Bacteroidetes* phylum associated with obesity (Mujico *et al*,2013; Parnell and Reimer, 2012; Ferrer *et al*,2013; Caricilli *et al*,2011).

However, several studies have demonstrated opposite results, where *Firmicutes* is decreased in overweight and obese humans, as well as in obese mice, with a corresponding increase in *Bacteroidetes* (Schwiertz *et al*,2010; Carvalho *et al*,2012; Henao-Mejia *et al*,2012).

Advice to the general populous about diet management alone, is not improving the statistics on the numbers of obese individuals. A diet low in fat and unrefined carbohydrates was shown to be less fattening than a diet high in fat, indicating the importance of diet and quality of caloric intake, irrespective of physical activity (Astrup *et al*,2000).

Dietary strategies which aim to reduce postprandial insulin response and increase fat oxidation, via a low-glycaemic index (GI) diet have been shown to have a prime position in the prevention and treatment of obesity and associated metabolic disorders (Munsters and Saris,2014).

Despite the availability of this knowledge of the effect diet has on the human phenotype and its dissemination, obesity is increasing. Obesity is believed to be an inflammatory condition and probiotic treatment may prove to be advantageous either alone or in combination with modern day pharmaceuticals.

The microbiota phyla *Firmicutes* and *Bacteroidetes* in the GIT are either Gram positive or Gram negative bacteria respectively, depending on cell wall structure and based on their Gram stain retention. These two kinds of cells are distinguished from each other based upon the presence or absence of an outer lipid membrane, which is a reliable and fundamental characteristic of bacterial cells. *Bacteroidetes* which are Gram negative bacteria, have lipopolysaccharides (LPS) in their cell wall, which is a molecule formed by a lipid and a polysaccharide. The LPS stimulate an immune response, promoting an inflammatory reaction, which is believed to protect the organism from bacterial infection (Akira and Takeda, 2004). Four weeks of mice fed a high-fat diet, resulted in an obese phenotype with the reduction of Bifidobacteria and Eubacteria species and an increase in circulating LPS levels, which Cani and co-authors named “metabolic endotoxaemia” (Cani *et al*,2007). LPS plasma concentrations were much lower than those observed during septic shock (Cani *et al*,2007).

When metabolic endotoxaemia was reproduced by subcutaneous infusion of LPS, metabolic abnormalities were induced by the high-fat diet. LPS receptor “knock out” mice (CD14KO) were resistant to the effects of both high-fat diet and LPS infusion (Cani *et al*,2008). The CD14KO mice were hypersensitive to insulin even when they were fed a normal diet, suggesting that CD14 might modify insulin sensitivity. Alteration of GIT microbiota composition by antibiotics reduced metabolic endotoxaemia and the caecal content of LPS, correlating with a reduction in the obese phenotype in both high-fat-fed and *ob/ob* mice (Cani *et al*,2008).

Lipopolysaccharides (LPS) appear to activate systemic inflammation in healthy human subjects. A high-fat, high-carbohydrate meal induced a significant postprandial plasma LPS elevation, accompanied by a similar level of endotoxaemia (Anderson *et al*,2007). This increased adipose tumor necrosis factor (TNF)- and interleukin (IL)-6 concentrations and promoted insulin resistance (IR), and an increased mononuclear cell expression of TLR-4, nuclear factor- B (NF- B), and suppressor of cytokine signaling-3 (SOCS-3), an adipokine involved in IR (Anderson *et al*,2007). These increases did not occur with a meal rich in fiber and fruit (Ghanim *et al*,2009).

Another dietary component associated with metabolic disorders and endotoxaemia is excessive fructose intake. Mice fed a high-fructose solution for eight (8) weeks showed a 27-fold increase in portal endotoxin levels, and a significant increase in plasma inflammatory cytokines, hepatic steatosis, and IR, compared with controls. The increase in these markers were reduced in fructose-fed TLR-4-mutant mice, suggesting the LPS-TLR-4 axis may modulate the harmful metabolic effects of excessive fructose intake (Spruss *et al*,2009).

This suggests that specific food groups increase LPS, which initiate an inflammatory response resulting in the pathogenesis of obesity.

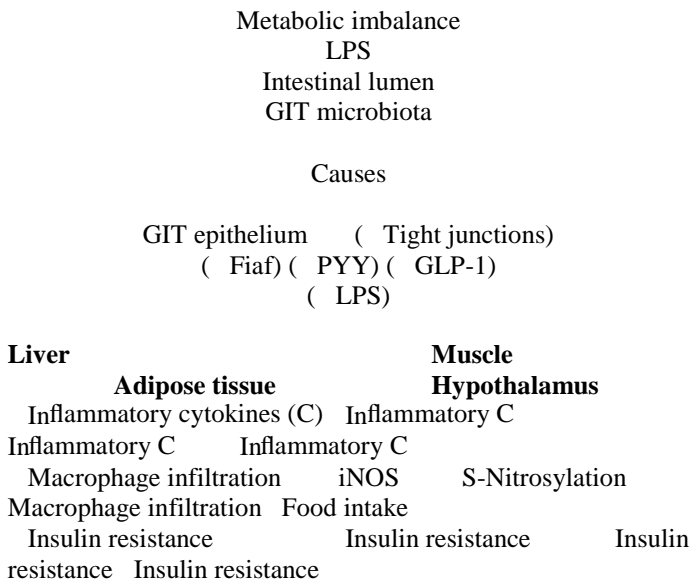
Lactic acid bacteria, belonging to the genus *Lactobacillus* and *Bifidobacterium*, have been shown to have beneficial effects on

health in critically ill patients, significantly reducing the levels of triglyceride (TG), and high-sensitivity C-reactive protein (hs-CRP) and increasing high density lipoprotein-cholesterol (HDL-C) levels(Sanaie *et al*,2013).

In the GIT, LPSactivateinflammatory responses via TLR4, which activates a cell signaling pathway inducing cytokine expression and secretion (Medzhitov *et al*, 2009). LPS levels are increased in obesity and type 2 diabetes increasing intestinal permeability (Creely *et al*, 2007;Mussoet *al*,2010).

This inflammatory response reduces the function and activity of tight junction proteins, zonula occludens-1 (ZO-1) and occludin, which in conjunction with the GIT epithelial cells, provide a barrier that separates the intestinal lumen and the microbiota and bacterial products from the peritoneal tissues and viscera. The reduction of tight junction function leads to the leakage of bacterial products, such as LPS, which are transported with chylomicrons into the general systemic circulation. This can then induce insulin resistance and inflammation in insulin sensitive organs(Carvalho *et al*,2013). (See Figure1).

**Figure 1**  
**Causative Factors of Inflammation**

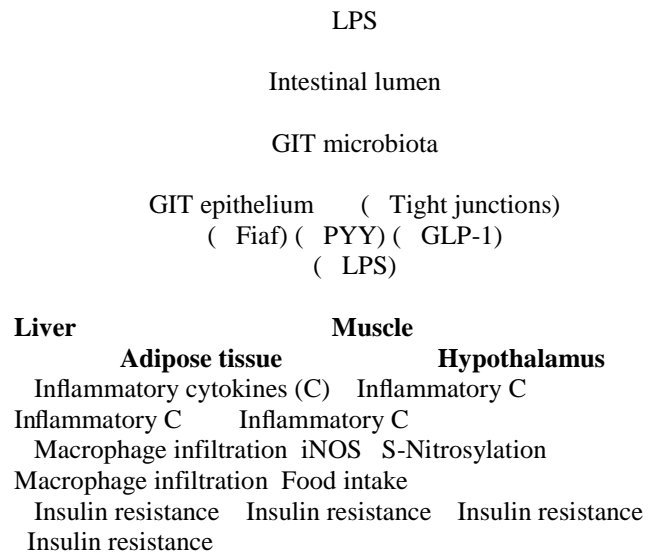


**Figure 1:** Dietary intolerance (excessive fat, refined carbohydrate, or fructose) alters the GIT microbiota. This initiates an immune response when bacteria migrate into the general circulation as result of increased intestinal permeability. Increased Insulin resistance in the hypothalamus increases food intake by decreasing satiety, increasing body weight. Consequential inflammation and immune cell infiltration of insulin sensitive organs induces insulin resistance supporting the obese phenotype.

**Key**

- C= cytokines
- Fiaf = Fasting-induced adipocyte factor
- GIT = Gastrointestinal tract
- GLP-1 = Glucagon-like peptide 1
- iNOS = inducible nitric oxide synthase
- LPS = lipopolysaccharides PYY = Peptide YY

**Figure 2**  
**Preventative Factors of Inflammation**  
Probiotic Bacteria (Antibiotics?)



**Figure 2:** Probiotics alters the GIT microbiota profile, and their metabolites (i.e., LPS, SCFAs).This reduces intestinal permeability and reduces bacterial products in the general circulation. Inflammation is reduced promoting increased insulin sensitivity. Decreased Insulin resistance in the hypothalamus reduces food intake by increasing satiety, reducing body weight.

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Research has been aimed at finding links between the composition of the microbiota, inflammatory responses and the metabolic pathways associated with obesity and type 2 diabetes mellitus (Furet *et al*,2010;Larsen *et al*,2010).

In mice fed with a high fat diet and Lactobacillus paracasei, the uptake of fatty acids from circulating triglyceride-rich lipoproteins is inhibited in white adipose and muscle tissues and ANGPTL4 (Fiaf)was found to be increased (Aronsson *et al*,2010).

Obese individuals when administered with Lactobacillus acidophilus NCFM showed a decrease in fat mass and insulin resistance and the risk of type 2 diabetes mellitus(See Figure1). However, the systemic inflammatory response was unaffected by the Lactobacillus acidophilus administration(Andreasen *et al*,2010).

The Bifidobacteria population (part of the Firmicutes phylum) is reduced in obesity compared to lean individuals with a corresponding increase in Bacteroidetes(Schwartz *et al*,2010).

A similar finding was reported in patients with type 2 diabetes mellitus in comparison with non-diabetic patients (Wu *et al*,2010).

*Lactobacillus gasseri* SBT2055 administration leads to a reduction in abdominal visceral obesity and BMI, an increase in insulin sensitivity in humans (Kadooka *et al*,2010) and *Lactobacillus Rhamnosus* GG, ATCC 53103 restricted excessive body weight gain in the first years of life of young children (Luoto *et al*,2010).

Probiotic strains produce many metabolites, enzymes, co-factors, and vitamins that improve our health. The fermentation of non-digestible carbohydrates (polysaccharides) by the GIT anaerobic microbiota and probiotics results in the production of short chain fatty acids (SCFA) such as acetate, propionate, and butyrate which are used as energy in the host (Tremaroli *et al*,2012).

Colonic epithelial cells, derive 60%-70% of their energy from SCFA. Butyrate, regulates cell growth and differentiation, and supports in reverting the cells from a neoplastic to a non-neoplastic phenotype (Salminen *et al*,1998).

Acetate is likely to be used as a cholesterol or fatty acid precursor, (Delzenne *et al*, 2002) and propionate is a gluconeogenic substrate (Al-Lahham *et al*,2010).

The intestinal structure and function is safeguarded by the microbiota it contains. The intestinal mucus layer (mucin) creates an obstacle to proinflammatory compounds and uptake of antigens (Kleessen *et al*,2005). Butyrate induces secretion of mucin, and antimicrobial peptides, which strengthens the protective barrier in the colon (Hamer *et al*,2008).

As previously stipulated, cell signaling, via the toll-like receptor (TLR) proteins, results in an inflammatory response initiated by LPS contact with cells, which protects the host from bacterial infection (Kawai *et al*,2005).

LPS from the GIT also reacts with saturated free-fatty acids (FFA), in the circulation of obese individuals resulting in liver lipogenesis and excess ectopic lipid accumulation (Miller *et al*,2005). In obesity and conditions related to increased intestinal permeability, TLR4 is known to be involved in the inflammatory response that can result in insulin resistance and the metabolic syndrome, which are prevented by the inhibition of TLR4 protein activity (Al-Samuel *et al*,2012, Kim *et al*,2012). A specific liver protein, fetuin-A (FetA), which is a carrier of FFAs in the circulation acts as a ligand of TLR4, causing insulin resistance. This was obstructed in the absence of FetA, reducing insulin resistance induced by FFA (Pal *et al*,2012). In obesity circulating levels of FetA are increased, correlating with body weight (Ismail *et al*,2012). Loss of body fat lowers FetA circulating levels returning them to normal in obese children (Reinehr *et al*,2008).

The inflammasome is a group of protein complexes that identifies stress signals. It results in caspase-1 activation and proinflammatory cytokine secretion resulting in cell death (Strowig *et al*, 2012). TLR4 and TLR9 agonists can induce

inflammation and insulin resistance. Newborn and adult mice can be infected by inflammasome-deficient animals and develop the same conditions resulting in non-alcoholic fatty liver disease (NAFLD) and chronic hepatic inflammation (non-alcoholic steatohepatitis, NASH) leading to enhanced hepatic tumour-necrosis factor (TNF)- expression that drives NASH progression (Henao-Mejia *et al*,2012; Elinav *et al*,2011). In obesity inflammasome proteins are activated in macrophages by LPS. The macrophages enter into the circulation due to increased intestinal permeability. TLR-induced activation of nuclear factor B (NF- B) regulates the macrophage inflammatory response (Schroder *et al*,2012).

Viral infections can also trigger a specific cellular signaling pathway that activates c-Jun N-terminal kinase (JNK), inhibitor of nuclear factor- B kinase subunit (IKK ), NF- B, and transcription of proinflammatory cytokines, which are mediators of insulin resistance (García *et al*,2006). Double-stranded RNA-activated protein kinase (PKR) protects against viral infections and is also linked to obesity and insulin resistance. PKR's phosphorylation is increased in high-fat diet fed mice, leading to activation of JNK (Hirosumi *et al*,2002). PKR is also activated by bacterial products, such as LPS (Hsu *et al*,2004).

TLR4 proteins also activate inflammatory pathways by GIT-derived LPS, which increases inducible nitric oxide synthase (iNOS) which causes insulin resistance and subsequent hyperglycaemia (Sugita *et al*,2002). In obesity, an increase in iNOS expression is also observed in insulin sensitive tissues, which promotes S-nitrosation/S-nitrosylation, where nitric oxide (NO) reacts with cysteine residues to form S-nitrosothiol adducts, which modify protein function (Stamler *et al*,1997). LPS induce S-nitrosation/S-nitrosylation of the insulin signaling pathway, insulin receptor (IR), insulin receptor substrate-1 (IRS-1), and protein kinase B/Akt (Akt), inducing insulin resistance in the liver, muscle, and adipose tissue (Shinozaki *et al*,2011; Carvalho-Filho *et al*,2005; Ovadia *et al*,2011) (See Figure 1).

The inhibition of iNOS reduces the S-nitrosation/S-nitrosylation of insulin signaling proteins, reducing inflammation and therefore increasing insulin sensitivity (Ropelle *et al*, 2013) (See Figure 2). *Lactobacillus reuteri* strain ATCC PTA 4659 partly prevented diet-induced obesity, possibly via a previously unknown mechanism of inducing liver expression of Carnitine palmitoyltransferase (Cpt1a). However there were no effects on inflammatory markers, blood cholesterol or atherosclerosis (Fåk *et al*, 2012).

Obesity is associated with variations in bacterial GIT microbiota, with what would appear to be a reduction mainly in Bacteroidetes. In one non-interventive study, GIT microbiota analysis demonstrated significant increases in *Lactobacillus* species in obese individuals and significant increases in *Methanobrevibacter smithii* in anorexic individuals (Armougom *et al*, 2009).

In another non-interventive study, GIT microbiota analysis was depleted in *Methanobrevibacter smithii* and *Bifidobacterium animalis*, but enriched with *Lactobacillus*

reuterii obesity. GIT microbiota composition at the species level is correlated to body weight and obesity (Million *et al*, 2012). *Lactobacillus reuteri* and *Lactobacillus sakei* were positively correlated with BMI. *Bifidobacterium animalis*, *Methanobrevibacter smithii* and *Escherichia coli* were negatively associated with the BMI (Million *et al*, 2013). Interpretation of this data and management of obesity is still open to question.

### Managing Obesity with Pharmaceuticals

As previously stipulated there are currently very few effective prescription medicines available to manage obesity, both in the UK and the US.

Orlistat (tetrahydrolipstatin), marketed in the UK as Xenical by Roche Pharmaceuticals, is the most prescribed medicine for weight loss. It is also sold over-the-counter as Alliby GlaxoSmithKline.

It prevents the absorption of fats from the diet by acting as a lipase inhibitor. This reduces caloric intake. It is intended for use in conjunction with a supervised reduced-calorie controlled diet.

Orlistat is the saturated derivative of lipstatin, a potent natural inhibitor of pancreatic lipases isolated from the bacterium *Streptomyces toxytricini* (Borgström, 1988). However, due to its stability, orlistat was chosen over lipstatin for development as an anti-obesity drug. The efficacy of orlistat in causing weight loss is limited. Data from short-term clinical trials over one year demonstrated that subjects who took orlistat lost 2.7 kilograms, or 2.9% more body weight than those not taking the drug over the same period (Padwal *et al*, 2004). However, orlistat was shown to cause gastrointestinal (GI) side effects.

Orlistat was found to reduce the incidence of type 2 diabetes, in obese people, with a BMI > 30 kg/m<sup>2</sup>. After 4 years' treatment, the cumulative incidence of diabetes was 9.0% with placebo and 6.2% with orlistat, corresponding to a risk reduction of 37.3% (Torgerson *et al*, 2004).

### Mechanism of Action

Orlistat works by preventing around a third of the fat that is eaten from being digested. This undigested fat is not absorbed and is passed out with the faeces. With the correct diet this may avoid gaining weight, but does not necessarily cause weight loss. Therefore a low fat diet and exercise is still recommended. Orlistat acts by binding covalently to the serine residue of the active site of gastric and pancreatic lipases, the enzymes that play an essential role in the digestion of dietary fat (triglycerides) in the GI tract, with very little activity against amylase, trypsin, chymotrypsin and phospholipases. When administered with fat-containing foods, lipase activity is blocked by orlistat which partially inhibits hydrolysis of triglycerides, thus reducing the subsequent absorption of absorbable free monoacylglycerides and free fatty acids which are excreted undigested. Only trace amounts of orlistat are systemically absorbed. The primary effect is local lipase inhibition within the GIT after an oral dose. The primary route of elimination is through the faeces. Orlistat's pharmacological activity is dose-dependent. At the standard therapeutic dose

(120 mg three times daily [t.d.s.] with main meals) administered in conjunction with a hypocaloric diet, the inhibition of fat absorption (approximately 30% of ingested fat) contributes to an additional caloric deficit. The standard over-the-counter dose of 60 mg inhibits approximately 25% of ingested fat. Higher doses do not produce more potent effects and lead to side effects (Guercioli, 1988).

Orlistat does not produce significant disturbances to GI physiological processes or to the systemic balance of minerals and electrolytes, when a low fat diet is adhered. It does not affect the absorption and pharmacokinetics of drugs with a narrow therapeutic index or medicines frequently used by obese patients (Guercioli, 1988). Common side effects are fatty stools if a high fat diet is maintained (steatorrhoea), or more frequent urgent bowel motions, flatulence and GI upset. In 2012, the US FDA approved for weight loss, the selective serotonin agonist "lorcaserin". This was the first approval since 1999. Lorcaserin has serotonergic properties and acts as an anorectic. Lorcaserin is a selective 5-hydroxytryptamine<sub>2C</sub> (5-HT<sub>2C</sub>) receptor agonist (Thomsen *et al*, 2008).

The 5-HT<sub>2C</sub> receptors are located almost exclusively in the brain, and can be found in the choroid plexus, cortex, hippocampus, cerebellum, amygdala, thalamus, and hypothalamus. The activation of 5-HT<sub>2C</sub> receptors in the hypothalamus is supposed to activate proopiomelanocortin (POMC) production and consequently promote weight loss through satiety. This hypothesis is supported by clinical trials and other studies. While it is generally thought that 5-HT<sub>2C</sub> receptors help to regulate appetite as well as mood, and endocrine secretion (Millan, 2005).

Lorcaserin has maintained weight loss of five percent (5%) after two years use compared with controls (Hoy, 2013). The drug is a controlled drug and can only be obtained by prescription in the US, but is not available from the NHS in the UK. However it is available online and can be purchased with a credit or debit card (<http://www.belviq.com/#isi>). Information for patients recommends physician notification if there is a history of heart valve problems, central nervous system symptoms, or altered mood state, demonstrating the possible side effects of this medicine (<http://www.belviq.com/#isi>).

Also in 2012 the FDA approved the combination pill phentermine plus topiramate. Phentermine (PHEN) is a noradrenergic agent and was previously withdrawn from the market, following cardiovascular side effects (Connolly *et al*, 1997). Topiramate (TPM) is a drug used as an anti-epileptic and antimigraine drug having effects on the CNS. It is thought to act as a -aminobutyric acid agonist that increases satiety.

In trials, the combination of the drug in low dose (3 mg PHEN plus 23 mg TPM) intermediate dose (PHEN 7.5 mg plus TPM 46 mg) and high dose (15 mg PHEN plus 92 mg TPM) have significantly improved systolic blood pressure (SBP) and diastolic blood pressure (DBP), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) levels, and fasting serum glucose relative to placebo. At a two year follow-up, phentermine plus topiramate reduced glycosylated haemoglobin (HbA<sub>1c</sub>) in patients with DM (Garvey *et al*, 2012). HbA<sub>1c</sub> serves as a marker for the average

blood glucose levels, over the previous 8 weeks prior to the measurement, as this is the half-life of red blood cells. An average weight loss of 8.1 kg and 10.2 kg, respectively was attained at the end of 56 weeks with PHEN 7.5 mg plus TPM 46 mg, and PHEN 15 mg plus TPM 92 mg (Gadde *et al.*, 2011). Future research in the pharmaceutical industry will focus on neurotransmitters (serotonin, noradrenaline, dopamine, and histamine), peptides (neuromedin U, urocortin, bombesin, amylin, galanin), hormones (thyroid hormone, growth hormone) and cytokines (ciliary neurotrophic factor) which play a very important part in feeding behaviour and energy expenditure (Morton *et al.*, 2006).

The brain controls energy homeostasis and body weight by integrating various metabolic signals.

The research into the pharmacotherapy of obesity has been stimulated by the discovery of the effect leptin has on obesity. Leptin, which is an adipose-derived hormone, conveys critical information about peripheral energy storage and availability to the brain. Leptin decreases body weight by both suppressing appetite and promoting energy expenditure. Leptin resistance, a primary risk factor for obesity, may result from impairment in leptin transport, leptin signaling, and a sophisticated neuroendocrine system to control energy balance by constantly monitoring energy storage, availability from adipose tissue, and dietary consumption (Morris and Rui, 2009). Leptin controls energy balance and body weight by regulating neuronal activity in the hypothalamus. Leptin decreases body weight both by suppressing appetite and by increasing energy expenditure. Leptin deficiency and genetic deficiency of functional leptin receptors (LEPR) results in morbid obesity and associated metabolic diseases. This has provided research into the exogenous administration of leptin, with little or no effect because of leptin resistance (Heysmsfield *et al.*, 1999). In addition to controlling energy balance and body weight, leptin (in conjunction with the hormones ghrelin and insulin) also plays an important role in the regulation of mood and emotion and the rewards of food and of eating behaviour (Foster-Schubert and Cummings, 2006; Murray *et al.*, 2014).

The pharmaceutical companies have developed newer medications, such as glucagon-like peptide-1 (GLP-1) receptor agonists, which suppress appetite and compared them to interventional gastric surgery. Bariatric (gastric band) surgery is very effective for the management of morbid obesity, but there are always associated risks with surgery. Twelve months after bariatric surgery treatment versus liraglutide (a GLP-1 receptor agonist), the average weight loss was 38 kg in the bariatric surgery patients, versus 5 kg in the medical treatment group. Glycaemic control improved in both groups but was greater in the bariatric surgery patients. The cardiovascular risk scores decreased in both groups, but remained higher in the medical treatment than in bariatric surgery patients. Of note, almost 60% of patients on liraglutide met the target of glycated hemoglobin < 7% (53 mmol/ml) and lost 5% of body weight (Cotugno *et al.*, 2014). New data from the P3a SCALE Obesity and Pre-diabetes trial was presented at Obesity Week 2014, the 2nd Annual Congress of The American Society for Metabolic and Bariatric Surgery and The Obesity Society. In the liraglutide 3 mg group, 92% of patients lost weight, in combination with diet and exercise, compared with 65% on the

placebo treatment in the 56-week study. Patients treated with liraglutide experienced weight loss of 9.2% compared with a 3.5% reduction in the placebo group. Patients who received liraglutide were also found to experience improvements in quality of life scores ([http://www.ukmi.nhs.uk/applications/ndo/record\\_view\\_open.asp?newDrugID=4884](http://www.ukmi.nhs.uk/applications/ndo/record_view_open.asp?newDrugID=4884)).

Treatment of 481 patients with liraglutide was associated with low therapy failure, good glycaemic response, weight loss, and improvement in systolic blood pressure and lipid profile. After 12 months, mean ( $\pm$  SD) changes were HbA<sub>1c</sub> -1.2% ( $\pm$ 1.4%), fasting plasma glucose -28.3 ( $\pm$  41.1) mg/dL, weight -3.5 ( $\pm$  5.8) kg, BMI -1.3 ( $\pm$  2.1), waist circumference -2.6 ( $\pm$  6.7) cm (all,  $P < 0.001$ ) (Lapolla *et al.*, 2015).

The new pharmacotherapies appear to be successful in lowering weight and cardiovascular risk factors, with lower adverse side effects. However the research in pharmacotherapy and weight loss should possibly concentrate on the anti-inflammatory effects of the newer therapies, because the incidence of obesity is definitely travelling in the wrong direction.

## CONCLUSION

In summary probiotics are believed to modify the balance of GIT microbiota, and their metabolites (LPS, and SFCA) in the maintenance of inflammatory response and promotion of weight loss. This modification supports an increase in tight junctions' expression and function, which reduces intestinal permeability and bacterial products and metabolites entering the systemic circulation. LPS circulating levels and inflammatory status in insulin-sensitive tissues are reduced, as well as muscle S-nitrosylation and liver and adipose tissue macrophage infiltration, promoting increased insulin sensitivity and the whole body metabolism. GLP-1 and peptide YY (PYY) circulating levels are increased after treatment with GIT microbiota modulators which together with the improvement in insulin sensitivity in the hypothalamus promote reduction in food intake by satiety mechanisms and in conjunction with the increased Fiaf expression, contribute to reduced body weight (Carvalho and Saad, 2013).

Probiotics are one of the fastest growing items on the functional food market today. They are an affordable health product, with overt benefits to health, including anti-inflammatory responses to adverse diet. They appear to have few side effects compared with pharmacotherapy. There is a prospective opportunity to reduce the cost of medication by applying combination therapy, which may eventually result in stand-alone probiotic treatment, when the correct combination of micro-organisms has been identified.

Animal models have demonstrated that GIT microbiota can modulate host organism energy homeostasis and adiposity through different mechanisms, e.g., energy production from the diet, LPS-induced inflammation, modulation of tissue fatty acid composition, and GIT-derived peptide secretion. An undisputed causal relationship between gut microbes and obesity needs to



be recognised in humans. Currently the opinion is that obesity is a result of GIT microbiota, Western diet, and inactivity.

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