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EXCEL Medical Bulletin

EXCEL Division of Blue Cross Laboratories

ADDRESSING THE BENEFITS OVER RISKS OF BLEEDING WITH (LIPONORM-ASP) ASPIRIN & STATIN

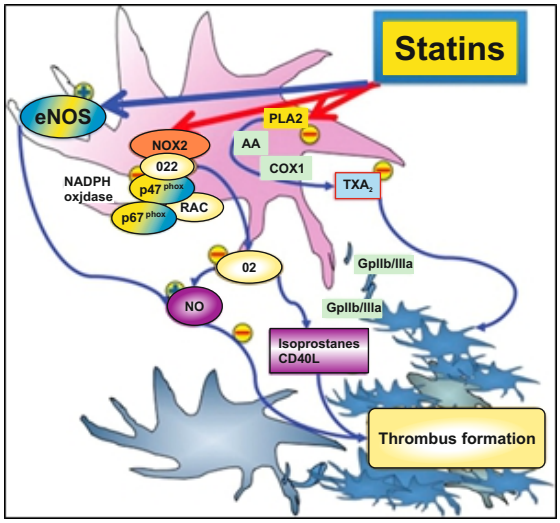
The pathophysiology of Acute Coronary Syndrome (ACS) in most patients involves atherosclerotic plaque rupture with a superimposed thrombus development resulting in limitation or interruption of coronary blood flow.

Aspirin is a non-steroidal anti-inflammatory drug (NSAID) shown to inhibit the formation of various inflammatory mediators and adhesion molecules results in the prevention of the progression of atherosclerosis.

Statins are a class of lipid lowering drugs that work by inhibiting the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase enzyme that is required for cholesterol synthesis and have a substantial impact on lipid lowering and delaying the atherosclerotic plaque development and progression.

It has been shown that the platelet response to Aspirin is reduced with increasing plasma cholesterol levels. It has been observed that hyperlipidemia primes the platelets & increases platelet activation. The oxidized low density lipoprotein (LDL) binds to the platelets leading to platelet activation & favoring thrombus formation. The concomitant use of statins could thus restore the normal platelet sensitivity to aspirin by decreasing cholesterol levels.

The hypothesized reason for the positive effect of statins in improving platelet response is related to their anti-inflammatory properties like decreasing the C-reactive protein, decrease in the activity of anti-inflammatory cells, decrease endothelial dysfunction by increasing the production of nitric oxide (NO) and decreasing the synthesis of endothelin-1.



Another hypothesis where statins potentiate the antiplatelet efficacy of Aspirin is that, unlike Aspirin, statins downregulate the platelet isoprostanes which are naturally occurring prostaglandin-like products that are produced by free radical mediated oxidation of unsaturated fatty acids that can cause thrombi formation at the sites of vascular injury through platelet aggregation.

Studies have shown that Aspirin reduces the risk of major cardiovascular (CV) events by 15-20% and statin therapy by 30-40% when used for primary prevention of cardiovascular disease (CVD). Therefore, in the prevention of primary CVD the combination of statins with Aspirin is more beneficial than Aspirin alone.

In order to reiterate this concept, the benefits of Aspirin and statins in combination on cardiovascular disease (CVD) have been tested in a meta-analysis of 5 RCTs which demonstrated a relative risk reduction for fatal and non-fatal MI were 29% and 31% respectively which were statistically significant.

The benefits of Aspirin and statins combination over each of the drug as monotherapy was greater than a simple arithmetic sum of the benefits of each agent suggesting a high probability of a synergistic benefit of aspirin and statin which could be attributed to the anti-inflammatory effects of both.

Additionally, the multifactorial etiology justifies the use of Aspirin and statin fixed-dose combination to increase treatment adherence as well as improve medical compliance by reducing the pill burden in patients.

However, Aspirin use is associated with an increased risk of major bleeding, intracranial bleeding and major gastrointestinal (GI) bleeding in both low and high CV risk populations.

A meta-analysis of 16 RCTs (171,215 individuals) showed that:

- When Aspirin was used in monotherapy vs a control, the incidence of myocardial infarction (MI) reduced significantly but also increased the risk of major bleeding.

- When statins were used as monotherapy vs a control, the chances of MI as well as the risk of major bleeding reduced significantly.
- When both were combined, the risk of MI among low risk and high-risk individuals was reduced.
- When both were combined, the risk of major bleeding did not reduce significantly but also did not show an increasing trend.

This concluded that addition of statins to Aspirin improved the risk of acute cardiovascular events and did not increase the risk of major bleeding and can be used safely as a combination in patients that require the same.

The addition of statins may also provide the opportunity of reducing the dosage of Aspirin that is required for prevention of primary and secondary CV events.

Source: Pillai KB et al. Int J of Scientific study 2020; 8(8): 154-163; Liu T et al. Scientific Reports 2023; 13(4585); De Beradis G et al. Trials 2007; 8(21); Hennekens CH et al. US Cardiology 2004; 1(1): 43-44; Khan SU et al. JACC Journals 2023; 2(2): 100197.

ROLE OF (K-MET) METFORMIN IN PREVENTING AGEING RELATED LEAKY GUT

The human microbiome that creates the human ecosystem is a collective ensemble of all the microbes, their genes and their environmental conditions found in and on the human body. Each individual has a unique microbiome that becomes typically unique with age reflecting the interactions throughout one's life.

The gut microbiome plays a crucial role in maintaining the host's local and systemic physiology including the gut homeostasis, nutrient metabolism, immunomodulation, metabolic activities and protection against pathogenic microorganisms.

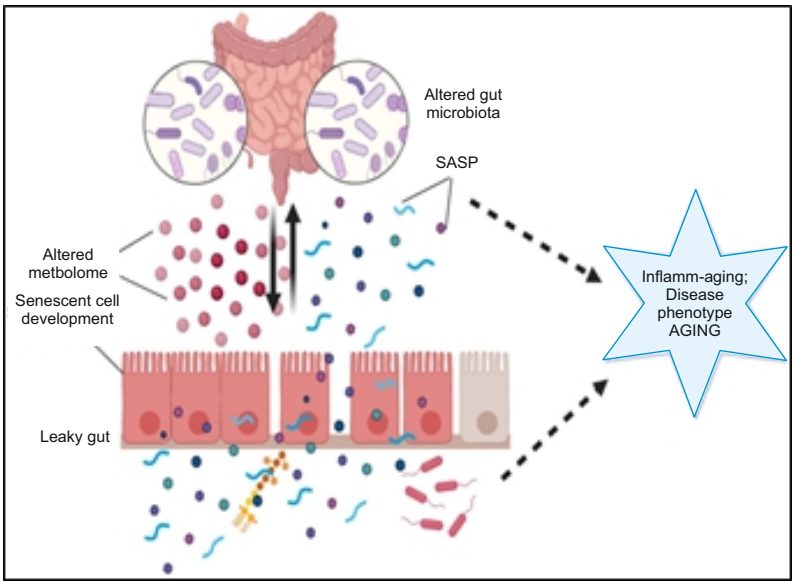
GUT MICROBIOME AND AGEING

The composition of the gut microbiota dramatically changes with ageing and is associated with the health and the lifespan of the host.

The abnormal gut microbiome and dysfunctional gut permeability (leaky gut) are linked with increased inflammation in older adults and these together remain a key risk factor for ageing related morbidities and mortalities.

Leaky gut

The intestinal mucus layer is primarily made up of mucin glycoproteins that are secreted by the epithelial goblet cells and covers the entire epithelia by forming a mucous gel layer that protects from invasion of antigens and regulates inflammatory responses.



Reduced thickness of this layer in the gut of the older adults is linked with the risk of impaired intestinal barrier function and inflammation.

Therefore, maintaining gut microbiome homeostasis and promoting mucin production in the gut can be an ideal target to reduce aging-related leaky gut and inflammation and promote healthy aging.Evidence indicates that leaky gut is often higher among older adults and obese individuals which is linked to chronic inflammation.

Inflammaging

Studies have reported that the age-related gut dysbiosis contributes to a chronic and an overall inflammatory state called inflammaging; specifically, through increased levels of pro-inflammatory molecules and cells like IL-6, IL-10, TNF-α, NF-kβ and mTOR.

It has been observed that in aged populations, there is a reduction in the number of intestinal commensal bacteria that maintain the immune tolerance in the gut and conversely opportunistic bacteria that stimulate inflammation tend to increase resulting in an inflammatory state.

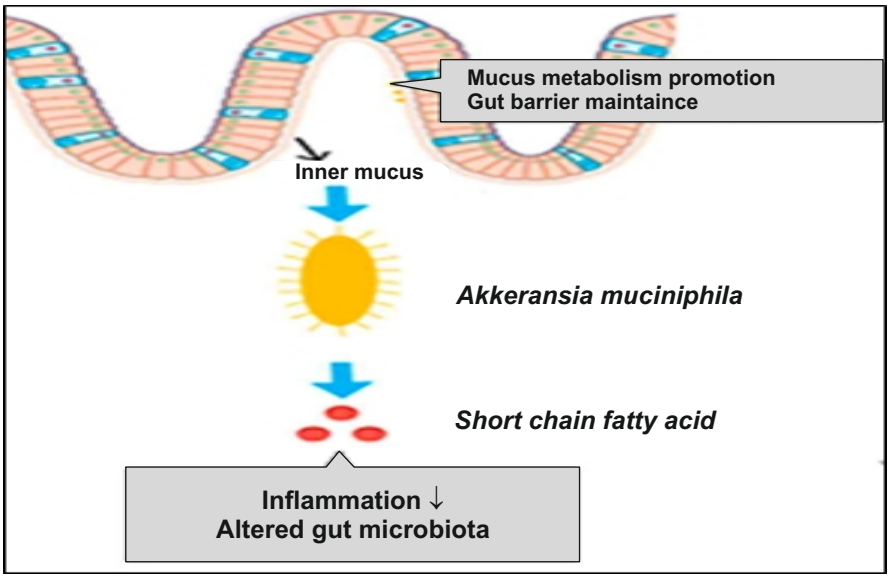
METFORMIN AND THE GUT MICROBIOTA

Metformin has been extensively used for the treatment of type 2 diabetes and additionally may also promote healthy ageing. Metformin has been implicated in the promotion and maintenance of a healthy gut microbiome and reduce many age-related degenerative pathologies.

The gut typically harbours thousands of bacterial species and as the concentration of Metformin is 100 to 300-fold higher in the gut as compared to the plasma, it is plausible that the microbiome-drug host interactions may influence the functional mechanisms of ageing.

Studies have indicated that Metformin has a beneficial effect on the modulation of the immune response by maintaining the expression of inflammatory markers like IL-6, IL-1β and TNF-α and on the gut permeability.

The hypothesized mechanism through which Metformin exerts these effects is via a bacterium, Akkermanisa muciniphila, a gram-negative anaerobe, accounts for 1-4% of the total gut microbiome, resides predominantly in the mucus layer of the colon where it is involved in maintaining the intestinal integrity by promoting mucus secretion and making the barrier mechanism more stable and therefor decreasing the epithelial permeability.



These bacteria metabolize un-absorbable carbohydrates and mucin in the short chain fatty acids which is used as fuel for the goblet cells. The stimulated goblet cells then produce mucin leading to the thickening of the mucus layer and decrease the epithelial permeability.

The expansion of A. muciniphila has been also shown to exhibit anti-inflammatory effects in the gut and reduce the colonic expression of proinflammatory genes and pathways.

METFORMIN AND AKKERANSIA MUCINIPHILA

Metformin has a number of actions within the gut. It increases the intestinal glucose uptake and lactate production, increases the GLP-1 concentrations and the bile acid pool within the intestine and alters the microbiome. Metformin treatment is shown to increase the population of A. muciniphila through the lactate production as it can be hypothesized that lactate & acetate in the gut may stimulate the growth of the same. Thus, Metformin treatment can be beneficial in the ageing gut with respect to the leaky gut and inflammation.

Metformin treatment has shown increase the population of A. muciniphila, thus leading to decreased epithelial permeability as well as reduce the IL-6, IL-1β mRNA levels in A. muciniphila leading to a decrease in the inflammatory state.

Additionally, Metformin is associated with an increase in the density of mucin producing goblet cells thus enhancing the mucin production.

In summary, the gastrointestinal epithelial barrier is affected by the physiological ageing process and restoring the barrier function becomes increasingly essential via the modifications in the gut microbiome. Metformin may prevent and treat ageing-related leaky gut and inflammation by beneficially modulating the gut microbiome/ goblet cell/ mucin biology.

Source: Induri NR et al. Annual Rev of Pharmacology & Toxicology 2022; 62: 85-108; Ahmadi S et al. J of Gerontology 2020; 75(7): e9-e21; Lee CB et al. Int J Mol Sci 2021; 22(7): 3566; www.intechopen.com/chapters/68972; McCreight LJ et al. Diabetologia 2016; 59: 426-435; Hagi T & Belzer C. Appl Microbiol Biotechnol 2021; 105(12): 4833-4811.

(MEGO XL) METHYLCOBALAMIN: THE PREFERRED SUPPLEMENT

Vitamin B12 or cobalamin is an essential nutrient that the body cannot produce and is necessary for the development, myelination and functioning of the CNS, healthy RBC formation and DNA synthesis.

The two most common forms of vitamin B12 supplements are cyanocobalamin and Methylcobalamin both of which can be converted to other forms in the body.

Methylcobalamin vs cyanocobalamin

Methylcobalamin is the naturally occurring biologically active form of vitamin B12 whereas cyanocobalamin is the synthetic biologically inactive form that gets converted to the active form in the liver. Sometimes the liver cannot convert cyanocobalamin to adequate amount of Methylcobalamin that is required and Methylcobalamin is the most bioavailable and readily absorbable form of vitamin B12 and hence a better choice for maximum bioavailability.

Cyanocobalamin has a cyanide group attached to its structure which needs to be removed and excreted from the body during its activation whereas Methylcobalamin has a methyl group attached to its structure and has cardioprotective benefits of the reduction of homocysteine levels. The methyl group of Methylcobalamin also stimulates serotonin creation, a neurotransmitter which is responsible for mood enhancement and protects the brain from damage against excitotoxins.

High homocysteine level is the main culprit for brain, vascular diseases, stokes risk and causes sclerosis in the arteries. Methylcobalamin converts homocysteine to methionine and reduces the potential to damage.

It also forms Adenosylcobalamin, the other form of vitamin B12 for mitochondrial energy production.

Methylcobalamin's urine excretion in humans is around one-third that of cyanocobalamin at the same dosage, which suggests increased tissue retention

Research has shown that Methylcobalamin is more efficiently used and retained in the body than the cyanocobalamin form.

Methylcobalamin is the superior form of vitamin B12 as it stays in the body for an extended period of time. It has a half-life of 6 days whereas cyanocobalamin has a half-life of 20-50 mins.

Given the facts, the verdict says that Methylcobalamin is the preferred supplement than cyanocobalamin being the active form, better absorbed and highly bioavailable with additional cardioprotective benefits.

Source: Paul C & Brady DM. Integr Med (Encinitas) 2017; 16(1): 42-49; https://holisticnootropics.com/methylcobalamin-vs-cyanocobalamin/; Nava Ocampo AA et al. Clin Exp Pharmacol Physiol 2005; 32(1-2): 13-8; Gupta JK & Sana QS. Austin J Pharmacol Ther 2015; 3(3): 1076; Singh K, et al. J. Appl. Microbiol. 2023; 7(2): 15

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