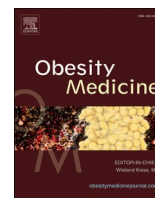




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## Gut microbiome dysbiosis and endotoxemia - Additional pathophysiological explanation for increased COVID-19 severity in obesity

### ARTICLE INFO

#### Keywords

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### ABSTRACT

The overall intestinal lipopolysaccharide (LPS) composition in the individuals with obesity could be shifted away from immunosilent/immunoinhibitory *Bacteroidetes* LPS subtypes, in favor of various proinflammatory LPS subtypes due to gut microbiome dysbiosis. What is more, high-fat diet, as well as obesity per se, enhance intestinal permeability through various mechanisms. Latter results in increased paracellular absorption and transcellular (via chylomicrons) transport of endogenous endotoxin in the circulatory system (endotoxemia). In addition, it is known that lipid A initiates a signaling cascade resulting in activation of various proinflammatory pathways and increases oxidative stress upon binding to toll-like receptor 4 (TLR4). Taking everything into consideration, it is very likely that gut microbiome dysbiosis and endotoxemia represent the additional pathophysiological explanation for increased COVID-19 severity in obesity.

Emerging body of literature indicates that individuals with obesity are more at risk for COVID-19 infection, as well as associated hospitalization, intensive care unit admission, and mortality (Popkin et al., 2020). Hence, an improved understanding of the pathophysiological interconnection between obesity and COVID-19 would definitely guide preventive and therapeutic strategies for this vulnerable population. Bearing this in mind, we have recently proposed obesity-related low-grade chronic inflammation, higher expression of ACE-2 and pathway associated components, and decreased vitamin D bioavailability as potential pathophysiological mechanisms leading to increased susceptibility and severity in obesity (Belančić et al., 2020). What is more, in the meantime, I have recognized gut microbiome dysbiosis and endotoxemia as additional plausible explanation for more severe forms of the COVID-19 infection among individuals with obesity, which then encouraged me to provide the present brief overview of the novel findings.

To clarify, lipopolysaccharide (LPS), commonly known as endotoxin, is a glycolipid found on the outer membrane of Gram-negative bacteria that is essential for bacterial cell integrity, viability, and defense against environmental stress. Latter amphiphilic molecule is composed of three structural domains: lipophilic lipid A (immunostimulatory component), hydrophilic polysaccharides or oligosaccharide core, and O-antigen. It is worth mentioning that the structure of lipid A is diverse among bacterial species, and that the number of acyl chains determines its immunostimulatory potential (Mazgaen and Gurung, 2020).

The overall collection ( $>10^{14}$ ) of microorganisms (bacteria, archaea, viruses, and eukaryotic microbes) colonizing the gastrointestinal tract is commonly known under term 'gut microbiome'. The human gut microbiota is mostly composed by two dominant (represent  $>90\%$  of the total community) bacterial phyla – *Bacteroidetes* (Gram-negative bacteria) and *Firmicutes* (mostly Gram-positive bacteria) (Qin et al., 2010). What is more, Eva d'Hennezel et al. reported that *Bacteroidetes* contribute 79% of the LPS biosynthesis in healthy volunteers and 92.4%

in Human Microbiome Project 1 samples, and that a total LPS produced in the healthy adult human gut is immunosilent/immunoinhibitory (has a very limited capacity to activate TLR4 - NF- $\kappa$ B pathway and elicit the production of inflammatory cytokines). Furthermore, underacylated lipid A structures across the order *Bacteroidales* are probably the main rationale for latter immunosilent/immunoinhibitory properties (d'Hennezel et al., 2017).

However, a relevant body of literature is generally consistent that individuals with obesity have a significantly higher level of *Firmicutes* and lower level of *Bacteroidetes* [increased *Firmicutes/Bacteroidetes* (F/B) ratio] compared to normal-weight/lean individuals (Ley et al., 2006; Koliada et al., 2017; Verdum et al., 2013). Hence, the intestinal LPS composition in the individuals with obesity could be shifted away from immunosilent/immunoinhibitory *Bacteroidetes* LPS subtypes, in favor of various proinflammatory LPS subtypes (phyla producing more inflammatory LPS) due to gut microbiome dysbiosis (d'Hennezel et al., 2017).

In addition, it is known that high-fat diet enhances intestinal permeability through various mechanisms: (i) alters the distribution and expression of tight junctions, (ii) stimulates a shift to barrier-disrupting hydrophobic bile acids, (iii) induces intestinal epithelial cells oxidative stress and apoptosis, (iv) stimulates proinflammatory signaling cascades directly and indirectly by increasing barrier-disrupting cytokines and decreasing barrier-forming cytokines, (v) negatively modulates the intestinal mucus composition and enriches the gut microflora with barrier-disrupting species (Rohr et al., 2020). It is also worth mentioning that Nagpal et al. even reported a close link between obesity-associated gut microbiome dysbiosis to cause derangements in the intestinal cellular turnover homeostasis and functions to regulate gut permeability, independent of dietary ingredients such as high fat (Nagpal et al., 2018). Thus, LPSs (endotoxins) could move into the circulatory system through direct diffusion due to intestinal paracellular permeability or via absorption by enterocytes during chylomicron secretion (Moreira et al., 2012). Its presence in the bloodstream is then called endotoxemia.

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**Abbreviations**

COVID-19	Coronavirusdisease 2019
LPS	lipopolysaccharide
NF-κB	nuclear factor-κB
SARS CoV-2	severe acute respiratory syndrome coronavirus-2
TLR4	tool-like receptor 4

Lipid A then initiates a signaling cascade resulting in activation of various proinflammatory pathways (predominantly NF-κB) and increases oxidative stress upon binding to TLR4 (Asehnoun et al., 2004; Boutagy et al., 2016). Last but not least, Petruk et al. in their preprint reported an interconnection between the S-glycoprotein of SARS CoV-2 and LPS, and their link to induction of NF-κB and cytokine responses in monocytes and human blood, as well as significantly increased NF-κB responses in experimental animal models (Petruk et al., 2020). Taking

**Declarations of interest**

None.

**Author contribution**

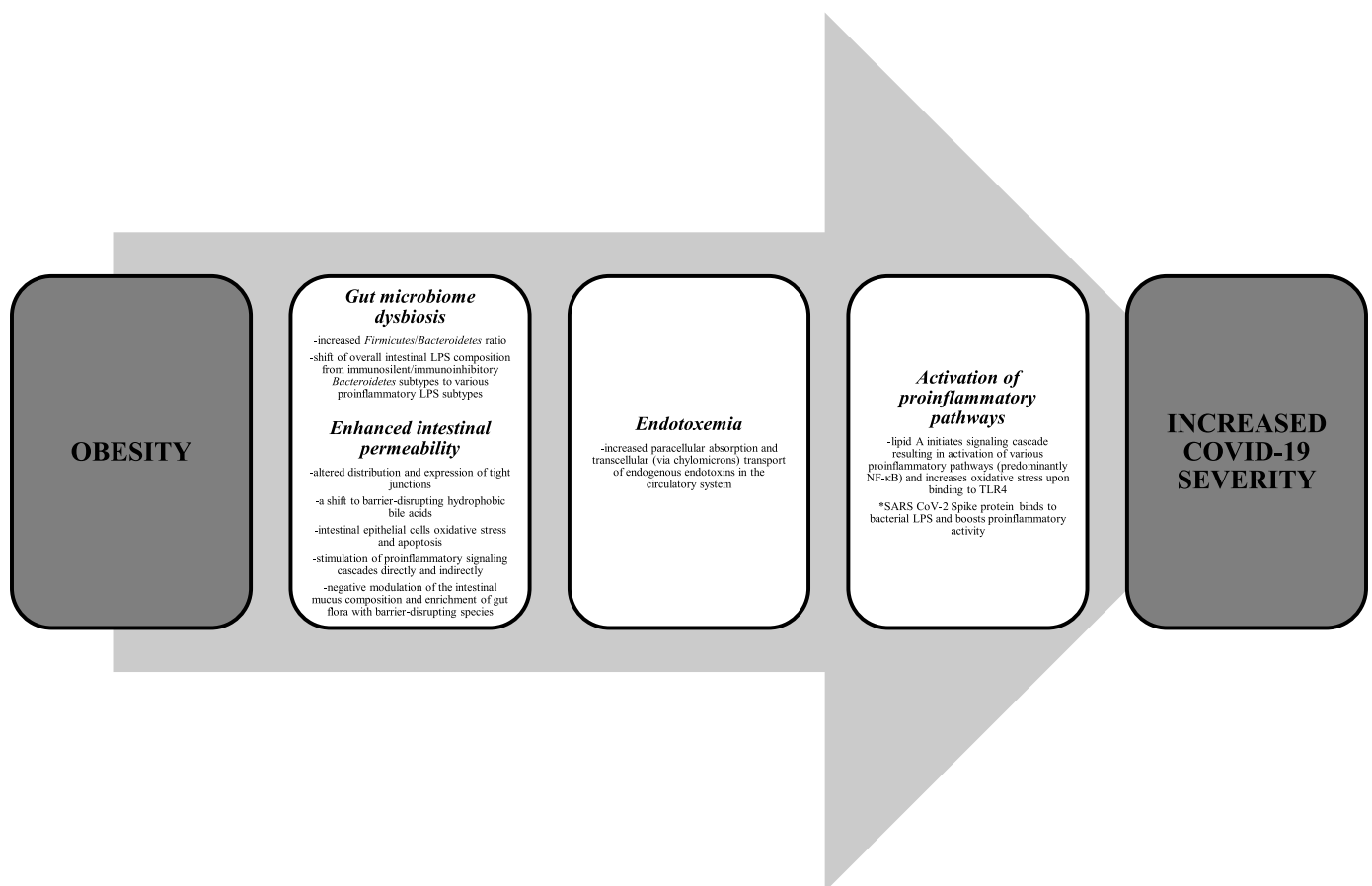
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**Declaration of competing interest**

The author of the manuscript (commentary) entitled **Gut micro-**



**Fig. 1.** The pathophysiological interconnection between gut microbiome dysbiosis and endotoxemia in obesity and increased COVID-19 severity.

everything previously mentioned into consideration, it is very likely that gut microbiome dysbiosis and endotoxemia represent the additional pathophysiological explanation for increased COVID-19 severity in obesity (Fig. 1).

To deduce, reducing caloric intake (especially trans-fat and saturated fat consumption) and modulating gut microbiota (with prebiotics/probiotics/synbiotics and anti-inflammatory dietary pattern) may reduce endotoxemia and consequently the associated risk for more severe forms of COVID-19 infection in obesity (Belančić et al., 2018). However, novel large-scale randomized controlled trials and well-designed meta-analyses are highly needed to draw final conclusions.

**biome dysbiosis and endotoxemia - Additional pathophysiological explanation for increased COVID-19 severity in obesity declares no conflict of interest.**

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