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Antibiotics; the Miracle Drugs, also a Predisposing Factor of Obesity

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ABSTRACT: We live in the era of antibiotics. This particular group of medicines has remarkable efficiency to treat infections with reduced morbidity and mortality and thus conquer the title of miracle drugs. But their enormous use without proper guidelines is a precursor of antibiotic resistance as well as is a raising concern of long-term metabolic changes in our body. In this review we emphasis on the impact of dysbiosis resulting from antibiotic exposure on body weight gain. Evidences tell us early life repeated exposures are unlikely to be a predisposing factor of offspring obesity. Pre-natal antibiotic use is also a contributory to this. Sex-specific effect is there: boys are more vulnerable compare to girls. Although the mechanisms underlining the association remain unexplained, the little we found out is this action is due to the byproducts of microbial fermentation, gut hormone alteration, metabolic entoxeamia and fasting induced adipocyte factor (Fiaf). Since randomized control trial (RCT) deals with the safety of the participants, it would be ethical concern in this regard and consumption of antibiotic doesn't show immediate effect on body mass index (BMI) while it usually increases the body fat at the later stages of life, additional well-designed longitudinal prospective cohort studies have been undertaken. More similar type of researches involving human regarding this issue necessitate for better explanation and ultimately to control the global epidemic obesity.

Keywords: Antibiotics, Dysbiosis, Obesity, BMI, SCFA, Bacterial components.

INTRODUCTION

The penicillin introduction by Alexander Fleming began the era of antibiotics, a compound produced by a microorganism possessing growth inhibiting or killing ability against other microbes and since then these have been recognized as the "miracle drugs" in the field of medical science. Right from invention they have been successfully used for treating different infections and to reduce morbidity and mortality (Rayanoothala *et al*., 2021; Tan and Tatsumura 2015; Zaffiri *et al*., 2012). Their remarkable effectiveness and easy availability make them famous worldwide but since their introduction, undoubtedly, they have been consumed freely and most of the time when they are not necessary (Del Fiol *et al*., 2018). So what happens usually, the innumerous use is followed by the dark side of the so called 'miracle drugs' (Shekhar and Petersen 2020). The bacterial communities are colonized in the human body, mainly in the GI tract plays an important role in metabolism and immunity of the host (Aversa *et al.*, 2021). Antibiotics target these microbiota, decrease their amount significantly even in some cases they completely remove specific bacterial community (Angelakis *et al.*, 2014) and hamper the gut-microbiota homeostasis (Shekhar and Petersen 2020). It has been hypothesized that this imbalance in gut microbiota, also known as dysbiosis is linked to overweight or obesity by different mechanisms especially due to the exposure of antibiotics at early stages of life (Leong *et al.*, 2018; Sejersen *et al*., 2019).

The term 'overweight' defined by WHO as BMI ≥ 25 kg/m^2 and 'obesity' as ≥30 kg/m^2, stand as the leading public health problem in current scenario (Vallianou *et al*., n.d.). Research evidences have shown the relationship between the abuse of antibiotics and the development epidemic obesity parallelly, during the last few decades. Now the epidemic has been transformed into a pandemic very fast (Del Fiol *et al.*, 2018). A commonly followed and most effective treatment procedure for obese individuals is the gastric bypass surgery. The change in the gut microbial composition after gastric bypass surgery has also been indicated to be connected to obesity. The high population of the family Prevotellaceae prior to surgery in obese individuals could be observed and following the surgery number of Prevotallaceae was reduced in lean subjects along with increase of the members of family Enterobacteriacae and genus *Akkermansia* strengthening the fact that change in gut microbiota composition has fair connection with gain and loss of weight (Zhang *et al*., 2009). Since antibiotic administration alters the gut microbiota composition, this review will emphasise on the effect of antibiotic consumption on body weight, intestinal gut microbiota,

and how dysbiosis occurs due to antibiotic exposure related to obesity.

Antibiotic use in the modern era. Unnecessary worldwide prescription and consumption of antibiotics have been reported in recent times by numerous studies- it may be considered as abuse these chemotherapeutic agents. One study demonstrate that there is an increase of 46% of global antibiotic consumption which rate from 2000 to 2018 (9.8 defined daily doses (DDD)/1000 population/day at 2000, 14.3 DDD/1000 population/day) in low income and middle income countries (Browne *et al*., 2021). According to The State of World's Antibiotic report in 2021, Global Antibiotic Consumption from 2000 to 2015 has been increased by 65% and if there is no alteration in this trend, it will be increased by 200% in the next 15 years. They also found that percentage change in per capita antibiotic use is 35.12% from 2010 to 2020 globally. In India, per capita antibiotic use is 5.74 DDD in 2020, whereas it was 4.40 DDD in 2010 (*The State of the World's Antibiotics 2021 A Global Analysis of Antimicrobial Resistance and Its Drivers*, n.d.). Children with same infection take different rates of antibiotics irrespective of their age, co-morbidities and socioeconomic factors. The overuse of antibiotics has been associated with antimicrobial resistance. World Health Organization (WHO) has identified this problem as "one of three greatest threat to human health" (Vangay *et al.,* 2015).

Development of gut microbiome. Human gut is crowded with heterogeneous microorganisms including bacteria, viruses, archaea, protozoa etc.(Leong *et al*., 2018). The initiation of introduction of microbes in human gut occurs during the birth i.e. at the time of delivery. The mode of delivery is the most predisposing factor for the development of gut microbiome as most of the microorganisms come from vagina, fecal sources and skin microbiome, along with the other factors like prematurity, infant diet (breast fed, formula fed), hygiene etc also contribute to the gut microbiome development (Vangay *et al.,* 2015). The initial pH of stomach ranges between 6-8 before birth and within the first hours of delivery decreases to ~1.5-2.5 but due to the buffering capabilities of milk it comes back to 7-7.6. This higher pH may support transition of ingested bacteria those colonized in the lower GI tract (Vangay *et al.,* 2015). Development of gut microbiome follows Darwin Dynamics where facultative aerobes colonize in the gut first reducing oxygen level in gut and enhancing the growth of strict anaerobes (Bezirtzoglou, 1997). Due to the introduction of breast milk as the first food for the infant, Proteobacteria and Firmicutes initially colonise in gut, followed by Actinobacteria (Sela *et al.,* 2008). There is a decline of *Proteobacteria* and Actinobactria and increase in the count of Bacterodetes by 6 months (Koenig *et al.*, 2011; Vaishampayan *et al*., 2010). At the age of 1 year, Bacterodetes and Firmicutes dominate infant gut. This dramatic change in the composition in gut microbiome continues throughout the first two years of life (Yatsunenko *et al.,* 2012). Firmicutes, Bacteriodetes, Proteobacteria, Fusobacteria, Spirocbaetae and Verrucomicrobia are the dominating bacteria in the adult human gut (Chan *et al*., 2013).

Effect of antibiotics on gut microbiome. The word antibiotic means against living organisms. These are the drugs used to treat infections either killing the bacteria or by inhibiting their growth and reproduction. So, it is obvious that they have an impact on the living things in the gut. Identification of the composition of this microbiome employs the modern genomic techniques since microbial culture technique possesses disadvantages like they can only identify a few species of bacteria in the intestinal gut. 16S rDNA and metagenomic sequencing are the modern techniques to know the composition and diversity of gut microbiome (Arslan, 2014). It is a culture independent analysis suited for viable but non-cultivable microorganisms and provides in-depth, extensive information of microbial community (Jo *et al*., 2016).

Bacteriodates and Firmicutes constitute approximately 90% of the total microbial content of gut (Arslan, 2014). Administration of Doxycycline and Hydroxychloroquine in endocarditis patients resulted in a decline in the concentration of Bactereriodates ($p=0.002$) and Firmicutes($p=0.01$) and also in total bacterial count. This phylum level gut alteration could play a key role in the weight gain (Angelakis *et al.,* 2014). Another study showed that children less than 3 years of age exposed with multiple antibiotic exposure courses causing less microbial diversity than the unexposed children (Yassour *et al*., 2016). Antibiotic type, consumer's age, route of administration can influence gut microbiome. Along with these the other contributory factors are diet, consumption of other medicines, lifestyles, probiotic consumptions etc. (Leong *et al.*, 2018).

Obesity is a global epidemic. Obesity, the global epidemic is a complex metabolic disorder resulting from the energy imbalance which can lead to excess accumulation of fat in our body. This is a risk factor for a number of significant co morbidities such as type 2 diabetes, hypertension, CVDs *etc.* at later stages of life. Most of the people live in those countries where obesity kills more people than underweight. Irrespective of socio economic status, the prevalence of overweight has increased dramatically over the past few decades. Since 1975 the worldwide obesity has nearly tripled (Goyal and Julka 2014; Huang *et al.,* 2010; Thompson-McCormick *et al.,* 2010). Over 340 million children and adolescents aged 5-19 were overweight or obese in 2016 globally (World Health Organisation). In India more than 135 million people were affected by obesity (Ahirwar and Mondal 2019). Since 2006, genome wide association studies have found 50 genes correlated with obesity. The thrifty gene hypothesis or Gianfranco's hypothesis was proposed by geneticist James V. Neel and said that in order to survive the famine we have procured efficient food and evolved genes for fat deposition. Rarely, obesity transpires in families according to an inheritance pattern due to change in a single gene. Generally, the implicated gene is MC4R,

which encrypt the melancortin 4 receptor. MC4R bound by alpha-melanocyte stimulating hormone that stimulates appetite (Walley *et al*., 2009). Although genetics play an important role, obesity epidemic does not have only genetic basis; lifestyle modifications during the last century has created an obesogenic environment that influence the genetic factor (Herrera and Lindgren 2010). Hence it is a metabolic disorder and it is very much associated with diet (Pitsavos *et al*., 2006).

Effect of microbiome on body weight. Gut microbiome has an effect on the physiological status of the host as it can influence the metabolism of the hosts (Arslan, 2014; Leong *et al.*, 2018). Low level of Bacteroidetes and high level of Firmicutes with reduced bacterial diversity in human intestine is associated with obesity (Arslan, 2014). Numerous randomized, double blinded placebo control studies were conducted at different parts of the world (Canada, Russia, Japan) on adult person who were overweight or obese or having metabolic syndrome. Results indicated that, when adults' diet supplemented with different species of probiotics, there had been a decline of body weight and fat mass (Sanchez *et al.*, 2014; Sharafedtinov *et al.*, 2013; Takahashi *et al.*, 2016). Similar kinds of findings were also found in the children. Nicolucci *et al*. (2017) treated overweight and obese children with oligofructose enriched inulin and after 16 weeks there was a reduction in body weight Z-Score (-3.10%) and body fat percentage (-2.40%) (Nicolucci *et al*., 2017). Biofidobacteria and members of *Lactobacillus* ssp. are found to be major candidates for managing the body weight and obesity in both human and experimental models. As a medication strategy use of *Lactobacillus* ssp. has been satisfactory owing to the fact that administration of it led to prolonged satiety and satiation including less fat deposition and food intake (Ameho and Christina 2021).

Antibiotic exposure can cause obesity. Animal and human studies provide supporting evidences that antibiotic use is associated with obesity though in this review we only focus on the human researches. Several epidemiological studies demonstrate that the use of antibiotics resulting in weight gain. Most of the studies done in this regards were either prospective or retrospective cohort and some were randomized control trials. Study findings indicate that the increase in BMI is more in boys and early life exposure has greater effect. Repeated exposure and broader spectrum of antibiotics are responsible for enhancing the BMI too. Undernourished children treated with Aureomycin shows significant difference in weight gain in the treated group with placebo group. Even prenatal antibiotic use also increases risk of obesity in their children (Table 1). This phenomenon is found in case of adults too, both in men and women. Ranitide and clarithromycin intake twice a day for 6 months increase the mean BMI of them. Patients of endocarditis, pulmonary diseases treated with different antibiotics (Vancomycin, Azithromycin, Doxycycline, Hydroxychloroquine etc.) put extra weight during the treatment (Table 2).

Table 1: Evidence showing the relation between early life antibiotic exposures and obesity.

Study	Studied subjects	Sample size	Study design	Exposure & Duration	Follow up	Outcomes	Remarks
(Macdougall, 1957) Africa	Undernourished African children (avg. Age 2 years)	n=72 38 received treatment, 34 placebo	Randomized Control Trial	Low dose of Aureomycin 50mg	2-7 weeks	Wight gain shows with highly significant differences Aureomycin treated-45.3gm/day Placebo treated-14.1gm/day	Yes
Aversa *et al*(Aversa et al., 2021) US	Children	n=14572 7026 girls, 7546 boys	Prospective cohort	Antibiotic exposure (< 2 years)	14 years	Overweight (12873 subjects, 4856 events, HR 1.22, 95% CI, p<0.001) Obesity (13649 subjects, 2567 events, HR 1.20, 95% CI, p<0.001)	Yes
Kenyon *et al*(Kenyon et al., 2020)UK, USA	Children from USA and Europe		Ecological study	Macrolides and total antibiotics consumption	5 years	Positively associated with obesity Europe- Coef 0.03, SE 0.005, p<0.001 USA- Coef 0.003, Se 0.0006, p<0.001	Yes
(Sejersen *et al*., 2019) Denmark	Mother-child cohort	n=700	Prospective cohort	Antibiotic exposure < 1 year	6 years	No association with BMI Z score -0.06 (95% CI: 0.17:0.06) No sex differences (p=0.48)	No
(Stark *et al.*, 2019) US	Children	n=241502	Cohort	Antibiotic exposure (in first 2 years of life)	7 years	Association with obesity (HR 1.26, 95% CI) Regardless to antibiotic class and strengthen with each class	Yes
(Zhang *et al*., 2019) North Carolina, US	Infants	n=454	Prospective cohort	Prenatal antibiotic exposure by their mother	12 months	2nd trimester exposure associated with higher infant WFL-z and skin fold thickness 0.21(95% CI 0.02, 0.41) higher WFL-z-at 12 months	Yes

						0.28(95% CI 0.02,0.55) higher WFL-z-second trimester exposure	
(Block *et al.*, 2018)	Children <72 months of age in 35 health care institutions	n=362550	Cohort	>=1 antibiotic prescription (before 24 months)	6 years	28% of study subjects develop overweight or obesity Body weight slightly increase (mean BMI Z-score 0.40[SD1.19])	Yes
(Cassidy-Bushrow *et al.*, 2018) US	Pregnant Women	n=303	Cohort	Antibiotic use (during pregnancy)	2 years	Prenatal antibiotic use associated with BMI Higher mean BMI Z-score 0.20+-0.10(p=0.046) 1st and 2nd trimester exposure were more strongly associated	Yes
(Ville *et al.*, 2017) USA	Latino children	n=97	Prospective cohort	Antibiotic use (infancy)	2 years	Weight gain (OR 6.42, 95% CI) Obesity at the age 2 years (OR 6.15, 95% CI)	Yes
(Poulsen *et al.*, 2017) Pennsylvania	Mothers and singleton children	n=8793	Cohort	Prenatal antibiotic use Antibiotic use of children (first 3 years)	6 years	Significantly associated with higher BMIZ in children Prenatal antibiotic use->=3 antibiotic order β[CI] (1 order:0.027, 2 order:0.034, >=3 order:0.117; p=0.006) 1st year antibiotic exposure->=2 antibiotic order β[CI] (1 order: 0.021, 2 order:0.088, >=3 order: 0.104; p<0.001) 2nd or 3rd year antibiotic use->=6 antibiotic order β[CI] (1 order: 0.015, 2-3 order: 0.053, 4-5 order:0.054, >=6 order: 0.123; p=0.003)	Yes
(Scott *et al.*, 2016) UK	Children of the health improvement network	n=21714	Retrospective cohort	Antibiotic exposure	4 years	↑ risk of obesity at 4 years (OR=1.21; 95% CI, 1.07-1.38) ↑ odd ratios with repeated exposures For 1-2 prescriptions (OR=1.07, 95% CI, 0.91-1.23) For 3-5 prescriptions (OR=1.41, 95% CI, 1.20-1.65) For >=6 prescriptions (OR=1.47, 95% CI, 1.19-1.82)	Yes
(Li *et al.*, 2017) California, USA	Infants in Kaiser permanent north California (born between 01.01.1997-31.03.2013)	n=260556	Retrospective cohort	Antibiotic use in infections	18 years	Infant with untreated infections antibiotic use not increase risk of obesity Infections without antibiotic use associated with obesity compared with controls without infections (OR=1.25, 95% CI) Neither broad spectrum nor narrow spectrum antibiotics associated with obesity	No
(Gerber *et al.*, n.d.) USA	Children with birth weight >=2000g	n=38614 (38522 singleton, 92 twins)	Retrospective cohort	Systematic antibiotic use (first 6 months)	7 years	Exposure not significantly associated with weight change Singleton children (0.7%, 95% CI, P=0.07) Twins (-0.09kg, 95% CI, P=0.30)	No
(Mbakwa *et al.*, 2016) Netherland	Children	n=979	Prospective cohort	Antibiotic exposure	10 years	One course antibiotic exposure ↑ weight (adjβ0.54, 95% CI) ↑height (adjβ 0.23, 95% CI) Later life exposure not	Yes/No

						associated Specific antibiotic use not associated	
(Schwartz *et al*., 2016) USA	Children aged 3-18 years	n=163820	Retrospective cohort	Antibiotic exposure	11 years	Short time BMI ↑ (p<0.001)	Yes
(Edmonson and Eickhoff 2017) USA	Children with vesicoureteral reflux (2-71 months with a median age 12 months)	n=607 antibiotic treated group=302; placebo=305	Randomized control trial	Trimethoprim-sulfamethoxazole-1 tab daily	2 years	No significant difference in weight gain between these two groups (change in weight for age Z-score SD +0.14[0.83]- in treated group; SD + 0.18[0.85]- in the placebo group)	No
(Saari *et al*., 2015) Finland	Boys and girls of first 24 months	n=12062	Prospective cohort	Antibiotic treatment		Exposed children heavier than unexposed BMI-for-Age Z Score Boys 0.13 SD, 95% CI, 0.07-0.19, p<0.001 Girls 0.07 SD, 95% CI, 0.01-0.13, p<0.05 Effect more pronounced after exposure to macrolides before 6 months of age Boys 0.28SD Girls 0.23SD >1 exposure Boys 0.20SD Girls 0.13SD	Yes
(Mueller *et al*., 2015) USA	Mother child dyads	n=436	Prospective cohort	Prenatal antibiotic use	7 years	85% higher risk of obesity with antibiotic exposure during 2nd & 3rd trimester ↑ BMI Z Score, waist circumference % of body fat (p<0.05)	Yes
(Mor *et al*., 2015) Denmark	School children	n=3250	Prospective cohort	Prenatal antibiotic exposure	11 years	Exposure associated with overweight (1.26, 95% CI) Obesity (1.29, 95% CI) Among girls (1.16, 95% CI)-for overweight (1.27, 95% CI)-for obesity Among boys (1.37, 95% CI)-for overweight (1.29, 95% CI)-for obesity	Yes
(Bailey *et al*., 2014) Philadelphia, Pennsylvania USA	0-59 months children	n=64580	Prospective cohort	Antibiotic exposure (during 0-23 months)	5 years	Cumulative exposure to antibiotics associated with obesity (RR 1.11, 95% CI)>=4 episodes Effect stranger for broad spectrum of antibiotics (RR 1.16, 95% CI) Early exposure 0-5m (RR 1.11, 95% CI), 6-11m (RR 1.09, 95% CI)	Yes
(Azad *et al*., 2014) Canada	Children from Canadian longitudinal birth cohort	n=1047 (at the age 9, n=616; at the age 12, n=431)	Prospective cohort	Antibiotic exposure (1st year of life)	12 years	Overweight later in childhood (P=0.002) Association persisted more in boys At the age 12-Boys (OR=5.35, 95% CI); Girls (OR=1.13, 95% CI) At the age 9-Boys (OR=2.19, 95% CI); Girls (OR=1.20, 95% CI)	Yes
(Murphy *et al*., 2014) International	Children of 38 centers of 18 countries	n=74946	Cross-sectional	Antibiotic-Paracetamol (first 12 months of life)	8 years	↑ BMI in boys (+0.107 kg m^{-2}, P<0.0001) No association in girls (-0.008 kg m^{-2}, P=0.75)	Yes/No
(Trasande *et al*., 2013) UK	Children birth weight >=2.5kg in avon	n=11532	Prospective cohort	Exposure of antibiotics at three different ages (<6months, 6-14months, 15-	7 years	↑Body Mass exposure of an, tibiotic<6months (↑ weight for length Z Score +0.105 s.d unit, P=<0.001 at 10 months	Yes/No

				23months)		+0.083 s.d unit, P=0.001 at 20 months BMI Z Score +0.067 s.d units, P=0.009 at 38 months) No association exposure of antibiotic at 6-14 months Positive association exposure of antibiotics at 15-23months (BMI Z Score +0.049 s.d units, P=0.050 at age 7 years)	
(Saiman *et al.*, 2003)	Cystic fibrosis patients >=6 years (87 active group, 98 placebo group)	n=185	Randomized control trial	Azithromycin 3 days in a week (for 168 days)	1.5 years	Average weight ↑ 0.7kg in patients than placebo group (95% CI, 0.1-1.4kg, P=0.02)	Yes
(Ajslev *et al.*, 2011) Denmark	Mother child dyads of Danish National Birth Cohort, infants before 6 months	n=28354	Prospective cohort	Antibiotic exposure	7 years	Children of normal weight mother, ↑ risk of overweight (OR 1.54, 95% CI) Children of normal weight mother, ↓ risk of overweight (OR 0.54, 95%CI) Children of normal weight mother, ↓ risk of overweight (OR 0.85, 95%CI)	Yes/No
(Saiman, 2010) US & Canada	Pediatric cystic fibrosis patients	n=260 Antibiotic treated group 131, placebo group 129	Randomized control trial (double blinded placebo control)	Azithromycin 3 days per week		↑ body weight (0.58 95% CI)	Yes

Table 2: Studies showing the association between antibiotic exposures in adulthood with obesity.

Study	Studied subjects	Sample size	Study design	Exposure &Duration	Follow up	Outcomes	Remarks
(Pirzada *et al.*, 2003) UK	Patients with pulmonary disease	n=40 20 patients 20 controls	Prospective cohort	Azithromycin 250 mg daily	12 months	↑ Body mass by a mean of 1.2 in the Azithromycin group	Yes
(Thuny *et al.*, 2010) France	Infected endocarditis patients	n=96 48 IE patients, 48 controls	Case Control	Vancomycin treatment	1 year	↑ BMI in treated group but not in controls (mean [+/- SE]kg/m^2, 2.3[0.9], p=0.03)	Yes
(Lane *et al.*, 2011) England, UK	20-59 years aged people	n=1558	Randomized Control Trial	Ranitidin bismuth citrate 400mg, Clarithromycin 500mg twice a day	6 months	Participants gain >=3kg in the intervention group compared to placebo group (OR 1.57, 95% CI) Mean BMI ↑ Intervention group:27.5-27.8 kg/m^2 Placebo group:27.0-27.2 kg/m^2	Yes
(Francois *et al.*, 2011) NewYork, USA	18 years adults and more	n=92 38 H. Pyolorie negative, 44 *H.pylori* positive, 10 interminate	Prospective cohort	*H. pylori* eradication therapy (Amoxicillin 1000mg, Clarithromycin 500mg, Omeprazole 20mg, Rabeprazole or Esomeprazole 20mg)	7 months	BMI ↑ (5 +- 2%, p=0.008) Post prandial acylated ghrelin ↑ 6 fold than pre-eradication (p=0.005) ↑ leptin 20% (p<0.001)	Yes
(Angelakis *et al.*, 2014) France	Q fever endocarditis patients	n=82	Prospective cohort	Doxycycline and Hydroxychloroquine treatment (for atleast 18 months)	1 year after treatment	Weight gain among 23% treated patients (P=0.001)	Yes
(Mikkelsen *et al.*, 2015) Denmark	Adult men 18-40 years	n=12	Intervention study	Antibiotic course with Vancomycin 500 mg, Gentamycin 40 mg, Meropenem 500 mg once in a day	1 year	Increase in body weight 1.3 kg (78.1-79.4), p=0.04 Increase in BMI 0.3 kg/m^2(22.6-22.9), p=0.04	Yes

				(6 months)			
(Mikkelsen *et al.*, 2015) USA	Women ages 35-74 years	n=50237	Prspective cohort	Penicicillins, Quinolones, Bactericidal, Tetracylines exposure		Antibiotic use during 4 th decade of life associated with obesity Penicillin (OR 2.00, 95% CI) Bactericidals (OR 1.71, 95% CI) Tetracycline	Yes

Association of antibiotic with obesity. The purpose of antibiotic use is to eradicate certain bacterial taxa; therefore, antibiotic exposures directly affect the gut microbial biodiversity leading to dysbiosis, which turn into predisposing factors of obesity by multiple mechanisms. Antibiotics-induced obesity primarily caused by shifts in functional capabilities of gut and then long lasting metabolic shifts resulting in irreversible recovery to the normal trajectory (Vangay *et al*., 2015). On the basis of animal and human studies several hypothesis have been made in this regard.

Byproducts of microbial fermentation. Microbial fermentation of indigestible polysaccharides yields short chain fatty acids (SCFAs) such as propionate, acetate, L-lactate, butyrate. These SCFAs play very crucial role in energy metabolism and adipose tissue expansion like acetate is used as a precursor of cholesterol and fatty acids and propionate acts as a neoglucogenic substrate (Delzenne *et al*., 2005; Delzenne and Cani 2011). SCFAs are ligands of G-protein coupled receptor GPR43 and activation of GPR43 inhibit lipolysis and differentiation of adipocytes (Arslan, 2014). Byproducts of microbial fermentation activate hepatic carbohydrate response element binding protein (ChREBP) increasing the transcription of regulators involving in lipogenesis, leading to accumulation of hepatic fat(Le Poul *et al.*, 2003). As microbial fermentation yields 80-200 kcal energy per day (Bell, 2015), change in the composition of gut microbiome i.e. 20% increase in Firmicutes with corresponding 20% decrease in Bacteroidetes count can create additional 150kcal energy on a regular basis, can be a contributing factor for gaining weight (Leong *et al*., 2018).

Alteration of gut hormones. Entero-endocrine system is regulated by gut microbial diversity like the abundance of Bifidobacterium though it is not the dominating phylum in gut but play an instrumental role on host metabolism (Arslan, 2014; Cani *et al.*, 2007). Dietary fructo-oligosaccharides increase the abundance of *Bifidobacterium* resulted into increased colonic fermentation as well as the level of glucagon like peptide (GLP-I) and decreased ghrelin (the hunger hormone), with subsequent decreased food intake and fat accumulation (Daubioul *et al.*, 2000; Delzenne *et al.*, 2005). Reduced *Bifidobacterium* and following a high fat diet yield increased secondary inflammatory activity, resulted in increase of fat mass and insulin resistance. SCFAs alter the secretion of Peptide YY (PYY) and GLP-I directly influencing satiety (Festi *et al.*, 2014). Reduction in PYY causes increase in intestinal transit time and reduction of harvesting dietary energy (Arslan, 2014). Gut bacteria induced bile acid metabolism that act as ligands of G-protein coupled bile acid receptor 1 and nuclear farnesoid X receptor (FXR). These two are also involved in gut hormone regulation related to glucose and lipid metabolism (Leong *et al*., 2018).

Metabolic endotoxeamia. Gut bacteria can disrupt the mucosal barrier of the gut and expose the host's immune system to microbial products like lipopolysaccharide (LPSs), lipopeptides that have hepatotoxic effects and induced inflammation called metabolic endotoxaemia. With increased permeability, endotoximia causes greater inflammation, a predisposing factor for weight gain. Gut microbiome have some microbe-associated molecules namely pathogen associated molecular patterns (PAMPs) and some endogenous products called damage-associated molecular patterns (DAMPs), those are noticed by pattern recognised receptor TLRs (toll-like receptors). Amongst the total 13 identified TLRs, TLR2, TLR4, TLR9 help in the development of non-alcoholic fatty liver disease (NAFLD). Bacterial components like LPS, flagellum, structural lipids, peptidoglycan create inflammatory response which ultimately lead to insulin resistance obesity (Abu-Shanab and Quigley 2010; Leong *et al.*, 2018; Machado and Cortez-Pinto 2012). It was observed that TLR4 led to inflammation, resulting weight gain in rats (de La Serre *et al*., 2010).

Fasting-induced adipocyte factor (Fiaf). Dysbiosis causes reduction of Angiopoietin-like protein factor 4 (ANGPTL4), also known as fasting-induced adipocyte factor, that inhibit lipoprotein lipase (Bäckhed *et al.*, 2004). Hindrance of lipoprotein lipase blocked the separation of fatty acids from triglycerides for tissue uptake and promote fatty acid oxidation-thus reduce fat storage (Mandard *et al*., 2004).

DISCUSSION

Though most of the studies implicit that the antibiotic exposure during infancy causing overweight or obesity in children in their later life (Bailey *et al.*, 2014; Saari *et al*., 2015; Scott *et al.*, 2016), some contraindication are there (Gerber *et al.*, n.d.; Sejersen *et al*., 2019). Overall the studies those found the association between antibiotic exposures with obesity for the children identified the early stage of life as the key period. Bailey *et al.* found that effect of antibiotic exposure in 0-5 months was stronger than the exposure in 6-11 months. Similar findings by Sarri *et al.* (2015) support this evidence, who found effect was more pronounced for exposure before 6 months of age (Bailey *et al.*, 2014; Saari *et al.*, 2015). This may be due to the reason

that infancy is the key period for microbial development in human gut. Azad *et al.* conducted a longitudinal study in Canada on antibiotic exposure during 1st year of life and note the results at 9th and 12th year. Similar kind of study was done by Sarri *et al.* (2015) on 6114 boys and 5948 girls. Both identified boys as a more vulnerable group for gaining more weight (Azad *et al*., 2014; Saari et al., 2015). Another thing is that the frequency of exposure of antibiotics. Scott *et al.* (2016) found that the odd ratio is more for >=6 prescriptions than 3-5 and 1-2 prescriptions, supported by the findings of Bailey et al. and Poulsen et al. (Bailey *et al*., 2014; Poulsen *et al*., 2017; Scott *et al*., 2016). An interesting finding came out from a Danish mother child dyads cohort study on early antibiotic exposure that, it was observed in the children of normal weight mother had increase the risk of overweight, where the risk of overweight was decreasing for the children of overweight or obese mother; indicating maternal pre-pregnancy BMI influence the body weight of their children in their later life (Ajslev *et al.*, 2011). In case of prenatal exposure of antibiotics where Muller et al. indicated that, antibiotic use during the last two had more impact on their children's body weight(Mueller *et al.*, 2015), Cassidy-Bushrow said 1st and 2nd trimester exposure was more strongly associated (Cassidy-Bushrow *et al.*, 2018). Another observation identify the second trimester exposure as the key period regarding this purpose (Zhang *et al*., 2019). There are many studies showing the clear association between antibiotic exposure in adulthood during treatment with weight gain (Angelakis *et al.*, 2014; Pirzada *et al.*, 2003; Thuny *et al.*, 2010) that indicate the consumption of antibiotic causing weight gain is irrespective of age but early life exposure has more impact on it.

CONCLUSIONS

This review has demonstrated that antibiotic exposure is a predisposing factor of obesity. Association is more marked for early life repeated exposures and particularly for the male child. We found out the children of the mother having a history of antibiotic use during pregnancy are also vulnerable. We are having still many unanswered questions such as class, dose, timing and mechanism. The little we know is use of antibiotics altering the biodiversity of gut microbiota and metabolites of them led to weight gain by their effect on body metabolisms. Randomized control trials would be unethical in this regards, further longitudinal human studies where these kinds of effects are secondary outcomes could elicit explanation.

FUTURE SCOPE

In this review article, the antibiotic exposure to children and consequent obesity was emphasised. Exposure to various types of antibiotics during early childhood and also antibiotic treatment to carrying mothers resulted in significant subsequent weight gain for the children after birth and in latter lives. In present scenario, this particular study may be significant since obesity is a global issue and this review shows that, right after birth of a child or even before birth administration of antibiotics is a cause of weight gain. Antibiotic may be more judiciously administered to control the weight gain and subsequent obesity in future. Further research is to be undertaken to correlate the antibiotic exposure during pregnancy and neonatal periods with other obesity induced diseases in their later lives.

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