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Short Communication

Possible Relationship between Zonulin, Metformin and Insulin Resistance in Polycystic Ovarian Women

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ABSTRACT

Zonulin protein is important to increase gut permeability, and its level is correlated with insulin resistance in polycystic ovarian women. Also, estrogen level is correlated with serum zonulin. Metformin, an insulin sensitizing drug can decrease serum zonulin in those patients. It is important to do new researches to know the mechanism of hormonal, and metformin effects on zonulin.

Keywords: Zonulin protein; Metformin; Gut permeability

DESCRIPTION

Zonulin is a haptoglobin precursor protein modulates the permeability of tight junction between cells of the digestive tract [1,2]. The increase of zonulin is associated with an increase in gut permeability; therefore Zonulin is suggested to have a role in the production of metabolic syndrome and insulin resistance [3]. Features of insulin resistance, sex hormone imbalance and infertility that accompanied polycystic ovarian syndrome which affect 3%-10% of women during their reproductive age [4-7], may be related to Zonulin level, as Zonulin is correlated with insulin resistance in those patients [8]. Moreover, irritable bowel syndrome and chronic fatigue syndrome, two conditions common in PCOS are linked to an increase in gut permeability [9,10]. The insulin-sensitizing drug, metformin that has many beneficial effects for polycystic ovarian patients may play a role in gut permeability due to its effect on gut microbiota by inhibition of bacterial complex I in a similar manner to metformin action on mammalian cell [11] or by another mechanism. We try to find if metformin has an effect on zonulin level.

It is found that 50% of metformin remain unabsorbed and retained in gut mucosa at 30-300 concentration folds than plasma concentration [12]. Metformin can delay absorption of glucose from intestine and increase production of Glucagon Like Peptide [13,14], and increase microbiota that produce short chain fatty acid that is important for insulin sensitivity [15,16], in addition to its insulin sensitizing effect in other tissue of the body [17,18].

Insulin resistance can be measured by different techniques, the most suitable non-invasion technique is measurement of homeostatic model assessment of insulin resistance (HOMA-IR), HOMA-IR=fasting insulin × fasting glucose divided by 22.5 [19-21]. A recent study for polycystic ovarian women showed that patients with (HOMA-IR) less than 2, exhibit no significant decreases in insulin and zonulin after three months of 850 mg metformin twice daily (Table 1), while polycystic ovarian women with HOMA-IR between 2 to 4 showed significant decrease in zonulin level p=0.01 and significant decrease in insulin level p=0.04 after three months of metformin treatment (Table 2), suggesting that metformin can decrease zonulin in insulin resistant patients only [22].

Table 1: Statistical analysis before and after metformin therapy in polycystic ovarian women with initial HOMA-IR<2.

		Mean+SD	P-value
Fasting insulin (uIU/ml)	Before	4.29+2.72	0.15
	After	9.13+10.11	
Fasting glucose (mg/dl)	Before	89.63+11.86	0.27

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	After	95.33+13.66	
HOMA-IR	Before	0.96+0.62	0.13
	After	2.43+2.93	
Serum zonulin (ng/ml)	Before	20.83+15.46	0.52
	After	16.90+15.21	

Table 2: Statistical analysis before and after metformin therapy in polycystic ovarian women with initial HOMA-IR=2 to 4.

		Mean+SD	p-value
Fasting insulin (uIU/ml)	Before	12.74+4.29	0.04*
	After	8.7+5.33	
Fasting glucose (mg/dl)	Before	89.73+24.2	0.06
	After	82.91+8.37	
HOMA-IR	Before	2.8+0.93	0.02*
	After	1.79+1.17	
Serum zonulin (ng/ml)	Before	16.26+10.10	0.01*
	After	7.92+5.09	

Note: *p-value less than 0.05.

However, Cetin suggested that insulin resistance is not triggered if there is integrity in gut permeability [23], while, Moghetti et al. revealed that metformin responders usually had higher fasting insulin [24]. The involvement of hormonal effect on zonulin and tight junction was approved by Zhou et al. study when they found that oestrogen has an inhibitory effect on certain protein expression important to strength tight junction [25], also according to another study, oestrogen showed a direct association with zonulin level in newly diagnosed polycystic ovarian women before starting metformin treatment (Figure 1) [26], which may be explained by that estradiol can decrease expression of protein zo-1 in tight junction and increase gut permeability leading to increase entrance of pathogen and giving rise to inflammation and expression of Interleukin 6 (IL-6), the latter can trigger more zonulin expression [27]. On the other hand, an another study showed that progesterone can decrease gut permeability by upregulating occludin protein an important protein in the structure of tight junction [28]. Recently, Ahmadi et al. find that metformin can treat aging-related leaky gut and inflammation, especially in obese individuals and people with high fat diet by beneficially modulating gut microbiome [29].

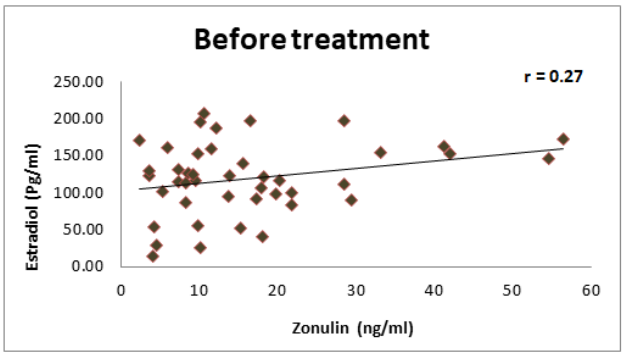

Figure 1: Correlation between Zonulin and Estradiol before starting treatment for patients with polycystic ovarian syndrome.

CONCLUSION

Metformin can decrease serum zonulin level may be due to its effect on microbiome or to its effect on oestrogen level or its enhancement of ovulation and progesterone production that strength tight junction, or by another undiscovered mechanism. Further studies are required to find possible mechanism of hormonal and drug effect on tight junction and zonulin in polycystic ovarian women and other people due to the greatest importance for gut permeability in enhancement of insulin resistance and initiation of chains of sequences for appearance of complication of this syndrome.

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