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Review Article

Incretin response in Asian type 2 diabetes: Are Indians different?

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ABSTRACT

Incretin-based therapy has clearly emerged as one of the most sought out strategy in managing type 2 diabetes, primarily because they generally do not causes hypoglycemia and possess weight-neutral or weight losing properties. Efficacy-wise too, these agents, are more or less similar to commonly used drugs metformin and sulfonylureas. Interestingly, some studies recently suggested that glycemic response to these incretin-based therapies could also differ ethnicity-wise. Subsequently, meta-analysis from these studies also suggested that Asians may have better response to these incretin-based therapies. This review will be an attempt to critically analyze those studies available in literature and to address as to why East-Asians and South-Asians may have different incretin response compared to non-Asians.

Key words: Adiponectin, DPP-4 activity, GLP-1 level in Asians, insulin resistance, incretin response, insulin secretory defect

INTRODUCTION

Current international diabetes federation (IDF) estimates indicate that 8.3% of adults (382 million people) have diabetes, and the number is set to rise beyond 592 million in less than 25 years. Close to one-fifth of all adults with diabetes in the world live in the South-East Asia region, of which 65.1 million of whom live in India, which could further increase to 109 million by 2035. India is the largest contributor to regional mortality, with 1.1 million deaths attributable to diabetes in 2013. The Asian region is of prime importance because it constitutes 60% of the world’s population. Asian population are also racially heterogeneous and have differing demographic, cultural and socioeconomic characteristics. The increase in type 2 diabetes in Asia differs from that reported in other parts of the world, as it develops in a much shorter time, in a younger age group and in people in a much lower body mass index (BMI). South-Asian type 2 diabetes patients are typically characterized by a relatively lower BMI but with higher amounts of visceral fat at given BMI or waist circumference, while East-Asians have predominant insulin secretory defect, when compared to their white counterparts. Nevertheless, the exact contribution of secretory defect and insulin resistance in the pathogenesis of Asian type 2 diabetes still remains elusive.

Reports from WHO multinational study, The Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (the DECODE) and in Asia (the DECODA) study revealed that both insulin resistance and insulin secretion capacity are higher in Caucasians. Although insulin resistance with obesity is the predominant patho-physiological defects in Europeans and Americans, impaired insulin secretion is major mechanism in East-Asians. Insulin secretory capacity has been shown to be half in Japanese type 2 diabetes compared to Caucasian patients, a difference that is particularly pronounced for meal-related secretion. The reasons for decreased insulin secretion in East-Asian patients with type 2 diabetes are yet to be determined but may be explained by lower beta cell mass, impaired beta cell function and genetic differences. These findings
observed primarily in East-Asians are in sharp contrast to findings which suggests, that young healthy South-Asian people are more insulin resistant and have significantly higher insulin level following a 6 hour oral glucose tolerance test (OGTT) compared to their Caucasian counterparts. There are significant differences in body composition between South-Asians and Caucasians. South-Asians typically have increased central obesity with thin limbs suggestive of smaller muscle mass, as evidenced by higher waist-to-hip ratio and greater sub-scapular: Triceps skinfold ratio. Interestingly, with the same BMI, visceral fat mass is higher in South-Asians compared with Caucasians. Consequently, South-Asians exhibits increased insulin resistance as demonstrated by fasting hyperinsulinaemia, reduced insulin sensitivity on OGTT and reduced glucose disposal during the euglycemic-hyperinsulinenic clamp study. A recent meta-analysis demonstrated that, there could be a hyperbolic relationship amongst Africans, Caucasian and East-Asians when insulin sensitivity index is kept on the X-axis and acute insulin response on the Y-axis. This study clearly revealed that Caucasian are located around the middle point of hyperbolic curve, while African and East-Asian are located around unstable extreme points of hyperbola and it is highly likely that a slightest change in one variable could lead to a large change in the other variables. It is also believed, that East-Asians have a limited innate capacity of insulin secretion which may decrease by progressive aging or beta cell exhaustion due to continuous ongoing insulin resistance. Therefore, it can be presumed that in East-Asians, even with slightest instability and vulnerability in canalization of beta cell, with a concomitant decrease in insulin secretion can easily promote diabetogenesis. This hypothesis may contribute to the increased prevalence of diabetes in Asia as a whole.

Interestingly, treatment response to medication could also be heterogeneous. Given the contribution of the insulin secretory defect and insulin resistance to the differences in the patho-physiology of type 2 diabetes between East-Asians, South-Asians and non-Asians, the response to certain anti-diabetic drugs including incretin-based therapies could also differ by ethnic groups. This review will be an attempt to critically analyze those studies available in literature and to learn as to why Asians may have different response to incretin-based therapies compared to non-Asians.

Ethnic differences in secretion and metabolism of endogenous incretin

There is no substantial clarity as to what happens to GLP-1 level on varying degree of dysglycemia. Literature also varied a lot on this issue. One of the very first and largest cross-sectional studies by Toft-Nielsen et al. demonstrated that the postprandial GLP-1 levels, the area under the curve (AUC) and the GLP-1 increments following a 4-hour mixed meal tolerance tests were significantly lower in type 2 diabetes, when compared to impaired glucose tolerance (IGT) or normal glucose tolerance (NGT) groups, albeit fasting GLP-1 were normal in all groups including type 2 diabetes. This study suggested a highly significant (53%) reduction in incremental GLP-1 concentrations and overall 19% reduction in the AUC in type 2 diabetes, compared to healthy controls. Subsequently, several other investigators also supported this finding and suggested a progressive decrease in GLP-1 level and GLP-1 responsiveness with worsening degree of hyperglycemia, starting from NGT to IGT to frank type 2 diabetes. However, some recent studies challenge those findings and point no changes in GLP-1 levels in either IGT or type 2 diabetes. Furthermore, two meta-analysis available also suggested no changes in GLP-1 level. Nevertheless, it should be noted that all these studies measuring GLP-1 level in varying degree of dysglycemia are not concordant and therefore, any conclusion regarding GLP-1 level still remains elusive.

Although the mechanism for these discrepancies is far from clear, several factors could be responsible for showing these diverging results. Sample size, sampling time, treatment influence, detection methods and diagnostic criteria of pre-diabetes or diabetes across the studies as well as course of disease can possibly influence the GLP-1 measurements. Age, body weight, non-esterified fatty acid (NEFA) and glucagon level can also influence the GLP-1 secretion. Taken together, it is apparently clear that only studies, which longitudinally assess GLP-1 secretion in pre-diabetic cohort followed until frank diabetes and subsequent progression over some years, can probably yield any substantial conclusion in this regard.

It should be noted, that ethnic differences may also be attributed to significant difference in fasting and glucose-stimulated GLP-1 levels among different races. From Asians perspective, data are even more conflicting as significant differences in total GLP-1, intact GLP-1 and GIP have been observed in some studies. Total GLP-1 level in Asians also varied from low to normal. A study by Yabe et al. showed negligible GLP-1 response after meal ingestion despite robust GIP response in both healthy and diabetic Japanese subjects. The reason for this reduced GLP-1 response is not exactly clear but may be explained by different meal size as well as meal composition (nutrient-induced) that may be sometime critical to GLP-1 response. In contrast, young healthy South-Asian showed higher GLP-1, higher

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Insulin level after a glucose load when compared to Caucasian counterparts. It still remains to be elucidated whether this higher GLP-1 response in South-Asians are due to a compensatory increased secretion or GLP-1 resistant state. Nevertheless, this study by Sleddering et al. suggested that peak GLP-1 levels preceded the peak insulin response and paralleled with insulinogenic index, thereby suggesting a direct relation between the increased GLP-1 response and the insulin secretion by the β-cell. 

Intact GLP-1 level were found to be considerably low in both Japanese type 2 diabetes and healthy controls, compared to Caucasians. The very low levels of intact GLP-1 can occur, due to either impaired secretion from the gut or accelerated metabolism by DPP-4, or both. Logically, any finding of low intact GLP-1 despite significant peak of total GLP-1 (following a glucose load) would hint toward a possible DPP-4-enhanced GLP-1 metabolism. Intriguingly, this study by Yabe et al. also showed a higher intact GIP: total GIP ratio, thereby implying that enhanced DPP-4 activity was selective to GLP-1. Although, it appears that GLP-1 is more liable to DPP-4 processing compared to GIP, further studies are really required to understand the basis of the selective reduction of intact GLP-1 in Japanese. Nevertheless, these data must be interpreted with caution in the light of different assay and methodology used to measure total GLP-1 or intact GLP-1 in these studies. Interestingly, total GIP level following a glucose load or mixed meal were higher in Japanese and levels of intact GIP were similar compared to Caucasians. This might suggests, a possible increase in processing of GIP by DPP-4 in Japanese. It should be noted that although the GIP response are enhanced in both Caucasians and Japanese type 2 diabetes (compared to healthy controls), the GLP-1 response in Japanese type 2 diabetes is significantly reduced. The reason for perceived enhanced GIP response in diabetic patients is not yet clear fully. Enhanced DPP-4 activities in type 2 diabetes have been observed by many researchers; nevertheless, these findings are discordant among individual studies. Some studies suggested increased DPP-4 activity, some unchanged and some decreased DPP-4 activity. However, a recent meta-analysis by Fadini et al. suggested a 33% enhanced DPP4 activity in type 2 diabetes. Therefore, it can be assumed that the reduction of postprandial active GLP-1 in type 2 diabetes could possibly be attributable to either impairment in GLP-1 secretion or an increase of its degradation (because of enhanced DPP-4 activity) or both. If the latter mechanism is found to be predominant in Asians as suggested by Lee and Yabe et al. and substantiated further, than it can be speculated that DPP-4 inhibitors might do a trick in East-Asians by suppressing enhanced DPP-4 activity.

In summary, as there is no significant difference in either GLP-1 or GIP levels between T2DM and healthy control, incretin deficiency does not seems to be accountable for the reduced insulin response in Japanese. Nevertheless, findings of low intact GLP-1 levels and low GLP-1 response after meals might have some correlation to reduced insulin secretory capacity and hence there could be exaggerated response to incretin-based therapies in the Japanese diabetic patients. Whether this finding from Japanese study can be extrapolated to South-Asians seems debatable. Also, very limited numbers of literatures are currently available on GLP-1 response in South-Asians. One study by Ahluwalia et al. suggested no significant differences in the gastro-intestinal mediated glucose disposal (GIGD %) between South-Asians and Caucasians. Therefore, we clearly need further studies to learn whether GLP-1 secretion could be similar or different in South-Asians compared to East-Asians or Caucasians.
Role of adiponectin and its relation to incretin response in Asians

Adiponectin is an adipokine, secreted exclusively by adipose tissue and has putative insulin-sensitizing, anti-atherogenic and anti-inflammatory properties. Total serum adiponectin concentration (all multi-meric isoforms) is inversely proportional to both visceral fat and insulin resistance. Low adiponectin has been found to predict the future development of incident type 2 diabetes in various populations including Pima Indian, Caucasian, Japanese, and native South-Asian people. Few studies consistently suggest that South-Asian have significantly lower adiponectin compared to Caucasian [Table 1].

Study from India, showed a typical association of low adiponectin in both type 2 diabetes and the metabolic syndrome. Another prospective Indian study also suggested that baseline hypoadiponectinemia independently predicted the future development of type 2 diabetes, after adjustment for covariates in IGT patients. All these data confirm that hypoadiponectinemia in South-Asians is clinically significant and plays a crucial role in the pathophysiology of insulin resistance and type 2 diabetes.

It is believed that the intervention to increase adiponectin level could provide benefit against atherosclerosis and diabetes. Activation of PPAR-γ by thiazolidinediones increases adiponectin at the transcriptional level and pioglitazone is a significant enhancer of adiponectin. Exendin-4 a GLP-1 receptor agonist, has shown to promote adiponectin secretion via the protein kinase-A pathway in high fat-fed rats. Few other experimental studies also showed that both GLP-1 agonist or DPP4 inhibitors increased serum adiponectin levels. Unfortunately, GLP-1 agonist-mediated increase of adiponectin still remains unknown in human. Interestingly, some data exist with DPP-4 inhibitors. An Italian multicenter, randomized, double-blind, placebo controlled trial, demonstrated that sitagliptin and metformin combination resulted in the significant increase of adiponectin, without change of body weight at 9 months. In contrast, other Italian multicenter, randomized, double-blind clinical trial assessing the effect of sitagliptin or metformin added to pioglitazone monotherapy in T2DM patients indicated, no change of adiponectin level by sitagliptin at 12 months. It is argued that sitagliptin-induced increase of adiponectin might have been masked by pioglitazone in this Italian study. A very recent randomized control trial in Japanese type 2 diabetes also showed sitagliptin increasing adiponectin without change of BMI. Another observational study also showed an increase in plasma adiponectin level after 12 weeks of sitagliptin treatment in Japanese T2DM. Recently, the 6 months treatment with vildagliptin has been found to increase adiponectin level.

Taken together, it can be presumed that the long term DPP-4 inhibitor treatment will likely elevate serum adiponectin levels and in turn reduce insulin resistance in South-Asians with predominant hypoadiponectinemia. This could possibly be another mechanism by which these incretin-based drugs might modulate different response in Asians with hypoadiponectinemia.

Response to incretin based therapy in Asians versus non-Asians

Ethnic differences in response to drug treatment, have been identified in the literature. Few individual studies [Table 2] and a meta-analysis primarily conducted in Asian subjects, hinted at better HbA1c reduction with incretin-based therapies, when indirectly compared with the results from phase 3 global trials, done primarily in Caucasian, African-American and Hispanic populations.

A randomized, double-blind, placebo-controlled, 18-week trial (n = 530) conducted by Mohan et al., evaluating efficacy and safety of Sitagliptin amongst Asian population (Korea, China and India) revealed significant glucose lowering (placebo-subtracted, -1.0%; P < 0.001) with Sitagliptin. Although, similar HbA1c reduction were noted in all three subpopulation relative to baseline, Indians and Koreans exhibited better HbA1c lowering (-1.4% each) compared to Chinese (-0.7%), against placebo. However, this appears to have occurred due to increase HbA1c in placebo arm in Indians (+0.7%) and Koreans (+0.6%) but decrease HbA1c in placebo arm of Chinese (-0.2%) patients. A 24-week, real-life observational study (n = 14) conducted by Kesavadev et al. evaluating efficacy and safety of Liraglutide in Indian patients showed remarkable lowering of HbA1c (-2.6%, P < 0.001), which appears to be quite higher reduction compared to what had been observed in six phase 3 global randomized Liraglutide

| Table 1: Adiponectin level in South-Asian versus Caucasians |
|-----------------------------------------------------------|
| **First author, year** | **Ethnicity** | **Adiponectin level** | **P value** |
| Valsamakis et al., 2003 | South-Asian: | Low | 0.016 |
| Raji et al., 2004 | Caucasian | Low | 0.05 |
| Abate et al., 2004 | South-Asian: | Low | 0.009 |
| Retnakaran et al., 2004 | Caucasian | Low | <0.0001 |
| Ferris et al., 2005 | South-Asian: | Low | <0.01 |
| Smith et al., 2006 | Caucasian | Low | 0.02 |
Table 2: Effectiveness of incretin-based therapies in Asians

| Author, year | Ethnicity | No. (wk) | Control | Active drug | HbA1c changes (%) | P value |
|--------------|-----------|----------|---------|-------------|-------------------|---------|
| Study with GLP-1 Agonist: | | | | | | |
| Seino et al., 2008 | Japanese | 226 (14 wk) | Placebo | Lira 0.1 mg to 0.9 mg/d | −0.72 to −1.67 (placebo +0.07−0.18) | NR |
| Gao et al., 2009 | China, India, Korea | 466 (16 wk) | Placebo | Exena 5 mcg BD to 10 mcg BD | −1.2 (Placebo −0.4) | NR |
| Kadowaki et al., 2009 | Japanese | 153 (12 wk) | Placebo | Exena 2.5 mcg BD to 10 mcg BD | −0.9 to −1.42 (Placebo +0.2) | NR |
| Iwamato et al., 2009 | Japanese | 30 (10 wk) | Placebo | Exenatide 0.8 mg QW to 2.0 mg QW | −1.0 to −1.5 (Placebo −0.4) | NR |
| Seino et al., 2009 | Japanese | 400 (24 wk) | Glibenclamide 1.25-2.5 mg/d | Lira 0.9 mg/d | −1.74 (Glibenclamide −1.18) | NR |
| Seino et al., 2009 | Japanese | 264 (24 wk) | SU | Lira 0.6 mg/d | −1.09 to −1.30 (Placebo+0.06) | NR |
| Kaku et al., 2010 | Japanese | 264 (20 wk) | Placebo | Lira 0.6 mg/d | −1.46 to −1.56 (Placebo−0.40) | NR |
| Kadowaki et al., 2011 | Japanese | 179 (24 wk) | Placebo | Exena 5 mcg BD or 10 mcg BD | −1.34 to −1.62 (Placebo−0.28) | <0.001 |
| Inagaki et al., 2012 | Japanese | 427 (26 wk) | Exena OD | Exena QW | −1.11 (Exena OD−0.68) | <0.001 |
| Seino et al., 2012 | Japanese | 267 (24 wk) | Placebo | Lira 0.6 mg/d | −1.00 to −1.27 than placebo | NR |
| Seino et al., 2012 | Japan, Korea, Philippines, Taiwan | 311 (24 wk) | Placebo | Lixi 10 to 15 and 20 mcg/d | −0.77 (Placebo+0.11) | <0.0001 |
| Study with DPP-4 inhibitors: | | | | | | |
| Iwamato et al., 2007 | Japanese | 363 (12 wk) | Placebo | Sita 25 mg to 100 mg/d | −0.69 to −0.96 (Placebo−0.28) | NR |
| Chan et al., 2008 | Chinese | 91 (12 wk) | Placebo | Sita 50 mg/d | −0.6 (Placebo−0.1) | NR |
| Maegawa et al., 2008 | Japanese | 134 (12 wk) | Placebo | Sita 50 mg/d | −0.4 (Placebo+0.4) | NR |
| Nonaka et al., 2008 | Japanese | 151 (12 wk) | Placebo | Sita 100mg/d | −0.65 (Placebo+0.4) | NR |
| Mohan et al., 2009 | Indian, Korean, Chinese | 530 (18 wk) | Placebo | Sita 100 mg/d | −0.7 (Placebo+0.3) | <0.001 |
| Kikuchi et al., 2009 | Japanese | 291 (12 wk) | Placebo | Vilda 10 mg BD to 50 mg BD | −0.8 to −1.2 (Placebo+0.2) | NR |
| NCT00411554 | Japanese | 319 (12 wk) | Placebo | Voglibose 0.2 mg TID | −0.7 (Voglibose−0.31) | NR |
| Seino et al., 2012 | Japanese | 312 (12 wk) | Placebo | Alo 12.5 mg/d | −0.59 to −0.65 (Placebo+0.35) | NR |
| Inagaki et al., 2013 | Japanese | 618 (52 wk) | Placebo | Metformin 2250 mg/d | −0.7 to −0.9 (Met−0.8 to −1.0) | NS |
| Takihata et al., 2013 | Japanese | 115 (12 wk) | Placebo | Pioglitazone 15 mg/d | −0.86 (Pioglitazone−0.58) | 0.024 |
| Zeng et al., 2013 | Chinese | 192 (24 wk) | Placebo | Lina 5 mg/d | −0.59 (Placebo+0.08) | <0.0001 |

WK: Week; NR: Not reported, NS: Not significant, Lira: Liraglutide, Exena: Exenatide, Exena GW: Exenatide once weekly, Lixi: Lixisentide, Sita: Sitagliptin, Vilda: Vildagliptin, Lina: Linagliptin, Alo: Alogliptin, Met: Metformin, BD: Twice daily

effect and Action in Diabetes study (maximum HbA1c reduction of -1.5% in LEAD-4 study). Interestingly, a 16-week double blind randomized study (n = 929) by Yang et al. suggested a similar glucose lowering with liraglutide among all Asians (Chinese, Koreans and Indians). Subsequently, a meta-analysis done from 62 randomized controlled trial by Park et al. suggested a better glucose-lowering effect of DPP-4 inhibitor in Asian compared to non-Asians (Asians: −1.67%; 95%CI, −1.89 to −1.44 versus non-Asians: −0.65%; 95% CI, −0.71 to −0.60; P < 0.05; Figure 3). Another recent meta-analysis done by Kim et al. also reported that both DPP-4 inhibitors (Asians: −0.92%; 95% CI, −1.03 to −0.82 versus non-Asians: −0.65%; 95% CI, −0.69 to −0.60; P < 0.001) and GLP-1 agonists (Asians: −1.16%; 95% CI, −1.48 to −0.85 versus non-Asians: −0.83%; 95%CI, −0.97 to −0.70; P = 0.044) were more effective in Asians compared to non-Asians when used in oral combination therapy [Table 3 and Figure 4]. Asian-dominant studies (studies with ≥50% Asians participants) clearly showed a greater HbA1c lowering effect than non-Asian-dominant studies (between-group difference for DPP-4 inhibitors: −0.18%, P = 0.006; between-group difference for GLP-1 agonist: −0.32%, P = 0.04),[83,86] Asian-dominant studies also suggested better fasting glucose reduction with DPP-4 inhibitor compared to non-Asian-dominant studies.[83] Univariate meta-regression analysis revealed a significant correlation of BMI with A1c reduction and Asian with lower BMI had better response with DPP-4 inhibitors. This significant correlation with BMI was also reported in other Japanese studies. Ironically, a recent two-nation wise audit database
from UK suggested lower incretin response and trends of lesser weight reduction with GLP-1 agonist in South-Asians compared to Caucasian.\[88]\[89\]

It is worth mentioning that this meta-analysis of Asian-dominant studies by Kim et al. mainly represents East-Asians and cannot be extrapolated to South-Asians, where insulin resistance contributes majorly. Heterogeneity in the studies included in these studies may also contribute to possible bias which is inherent to any meta-analysis and therefore these results should be interpreted cautiously.

**CONCLUSION**

It is apparently clear that pathogenesis of type 2 diabetes may have different underlying mechanism between Asians and non-Asians. Even among Asians, etio-pathogenesis could be different between East-Asians and South-Asians. While insulin resistance could be major mechanism for Caucasian, Europeans and South-Asians; insulin secretory defects seem to be underlying predominant mechanism in East-Asians. Hypoadiponecinemia could be another emerging mechanism for type 2 diabetes in South-Asians.

Although literature intriguingly varied about GLP-1 secretion with progressive dysglycemia, two meta-analyses from these studies suggest no significant deterioration in GLP-1 secretion. Ethnic differences in GLP-1 secretion are another important factor. Amplitude, responsiveness and pattern of GLP-1 secretion following a meal may also differ in different ethnicity. Difference in meal size and composition can also influence GLP-1 enhancement. Lesser intact: total GLP-1 in East-Asian may suggest enhanced DPP-4 activity. Taken together, these theories may suggest a differential impact of incretin-based therapies in East-Asian. On the other hand, South-Asians doesn’t show similar characteristics secretory defect seen with East-Asians, however, further studies are clearly required to understand differential GLP-1 response among all Asians.

Hypoadiponecinemia have been demonstrated unequivocally in South-Asians and suggested to be critically responsible for ensuing insulin resistance. Long-term uses of DPP-4 inhibitors have been found to be associated

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**Table 3: Effectiveness of incretin based therapies in Asian versus non-Asians: Meta-analysis**

| First author, year (trials included) | % A1c changes in Asians (95% CI) | % A1c changes in Non-Asians (95% CI) | P value |
|-------------------------------------|----------------------------------|-------------------------------------|---------|
| **DPP-4 inhibitors**                |                                  |                                     |         |
| Ezenatide BD 10 mcg BD              | -1.67 (-1.89 to -1.44)           | -0.65 (-0.71 to -0.60)             | <0.05   |
| Liraglutide 0.9 mg OD               | -1.85 (-1.60 to -1.5)            | -0.48 (-0.43 to -0.79)             |         |
| Sitagliptin 100 mg OD               | -1.4                             | -0.70 (-0.75 to -0.65)             |         |
| Vildagliptin 50 mg BD               | -1.4                             | -1.0                                |         |
| **DPP-4 inhibitors**                |                                  |                                     |         |
| Park et al., 2012 (62 RCT, 7 Japanese and 55 non-Japanese) – meta-analysis | -1.67 (-1.89 to -1.44)           | -0.65 (-0.71 to -0.60)             | <0.05   |
| **Kim et al., 2013 (55 RCT) – meta-analysis** | -0.92 (-1.03 to -0.82)           | -0.65 (-0.69 to -0.60)             | <0.001  |
| Between-group difference: -0.18%    |                                 | 0.006                               |         |
| **GLP-1 Agonist**                   |                                  |                                     |         |
| Kim, et al., 2014 (15 RCT) – meta-analysis | -1.16 (-1.48 to -0.85)           | -0.83 (-0.97 to -0.70)             | 0.044   |
| Between-group difference: -0.32%    |                                 | 0.04                               |         |

NR: Not reported, *This meta-analysis of Asian studies compared the results with individual study done in non-Asians, CI: Confidence interval, BD: Twice daily, OD: Once daily, RCT: Randomized controlled trial
with an enhancement in adiponectin levels in some of Italian and Japanese studies, however, no studies have been conducted so far in South-Asian, so as to suggest that enhancement of adiponectin by DPP-4 inhibitors could make any differential impact on them.

Nevertheless, clinical trials comparing effect of incretin-based therapies indirectly hint a significant and exaggerated response to incretin-based therapies in Asians (mainly comprising East-Asians) compared to non-Asians. Although the exact reasons for better response to incretin-based therapies are not yet fully known but this might be explained by the fact that East-Asians are less obese and possess “thrifty” genotype, which probably ensures more insulin secretory defects compared to non-Asians and hence these agents could be more effective. However, whether these results can be extrapolated to South-Asians or Indians is not yet known and neither has been demonstrated through any dedicated studies so far. A prospective study involving different ethnic groups may enlighten these possible differences in incretin response if at all it exists.

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