The Role of Statins (HMG-CoA Reductase Inhibitors) on Insulin Secretion from the Islets of Langerhans: A Systematic Review
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Abstract

Context: Statins are administered to decrease atherosclerosis in patients with coronary heart disease. These drugs enhance the risk of diabetes by affecting islets insulin secretion.

Objectives: Therefore, this systematic review investigates the effect of statins on insulin secretion of islets of Langerhans in the related original studies.

Methods: A preliminary search was performed in the PubMed, Scopus, Web of Science, and ProQuest databases. The search strategy terms were statin (hydroxymethylglutaryl-CoA reductase inhibitors), insulin secretion, and islets of Langerhans. The search elements were evaluated using the Mesh term system. Limits were used to include only review articles and no limits were set on language. The quality of the method and risk of bias was assessed by its tool.

Results: After removing irrelevant articles to the subject, 20 articles fulfilled the inclusion criteria. In vivo studies revealed that pravastatin and rosuvastatin increase and decrease islets insulin secretion, while atorvastatin and fluvastatin reduced this variable, and pitavastatin had no effect. The results of in vitro studies showed that pravastatin and induced both increasing and decreasing effects on insulin secretion from the pancreatic islet cells. Also, administration of atorvastatin, rosvastatin, fluvastatin, pitavastatin, simvastatin, and lovastatin decreased islet insulin secretion in the medium.

Conclusions: Pravastatin could enhance pancreatic islet insulin secretion while other statins reduced this variable. Finally, the contradictory effect of statins on islets’ insulin secretion can indicate the existence of laboratory and clinical research in this regard.

Keywords: Hydroxymethylglutaryl-CoA Reductase Inhibitors, Islet of Langerhans, Insulin Secretion

1. Context

At first, statins were known as new antibacterial drugs, and from 1976, it was revealed that this category of drugs is the inhibitors of hydroxymethylglutaryl-CoA (HMG-CoA) reductase. Statins are widely administered to decrease atherosclerosis via reducing plasma levels of low-density lipoprotein cholesterol (LDL-C) in patients with dyslipidemias and coronary heart disease (1, 2). Statin medications consists of Atorvastatin, Simvastatin, Lovastatin, Mevastatin, Pravastatin, Fluvastatin, Cervastatin, Pitavastatin, and Rosuvastatin (3). The justification for the use of statins in prevention (JUPITER) study indicated that the administration of statins increases insulin resistance in animal models and patients, and approximately enhances 20 - 30% risk of diabetes (2). Type 2 diabetes development caused by statins reduces insulin secretion of islets of Langerhans. However, the mechanism of this event remains unclear, but some studies showed that “statins diminish pancreatic β-cell function via Ca²⁺ signaling pathways impairment, compromise insulin signaling and down-regulating of insulin-responsive glucose transporter 4 (GLUT-4) (4). It was revealed that elimination of HMG-CoA reductase in a β-cell exhibited hypoinsulinemic hyperglycemia due to reduces in both β-cell mass and insulin secretion (5). One study reported that simvastatin as an (HMG-CoA) reductase inhibitor decreases insulin secretion in MIN6 β-cells through inhibition of acetylcholine receptor activity, free fatty acid receptor 1, and calcium release from intracellular stores (6). Moreover, contradictory results have been obtained regarding the effect of statins on insulin secretion from the islets of Langerhans. Some of them believe that these drugs increase insulin secretion (7) and the others show a reduction in insulin secretion from the islets (8). Therefore based on the effect of statins in the development of diabetes by reducing or increasing insulin secre-
tion, we performed a systematic review of animal, cell, and human studies investigating the effect of statins administration on insulin secretion of islets of Langerhans.

2. Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (9).

The electronic literature search was done in the databases Medline (PubMed), Scopus, Web of Science, and ProQuest.

2.1. Search Strategy

All electronic databases were assessed from 2000/01/15 until 2021/12/15. The search strategy for the PubMed database is exhibited in Table 1, and the other databases were attached to this article as appendix 1-3. The search strategy terms were consisted of three elements: (1) statin (Hydroxymethylglutaryl-CoA reductase inhibitors); (2) insulin secretion, and (3) islets of Langerhans, and were used in combination with each other. The search elements were evaluated by the controlled vocabulary terms called Mesh Term system. Limits were used to include only review articles and no limits were set on language.

2.2. Inclusion Criteria

Type of publication (article, book, and pepper conference), all language, and type of study (original studies) performed from 2000/01/15 until 2021/12/15 in each country and examines the relationship between Statin, Insulin secretion, and Islets of Langerhans were addressed as inclusion criteria in the present study.

2.3. Article Selection

All of the articles were transferred to EndNote (X8) software in the search phase. At the screening stage, the researcher independently reviewed the title and abstract of the articles that fulfilled the selection criteria. During this phase of the study, two independent authors have assessed the selected article (according to the PRISMA flowchart) to ensure that they satisfied the inclusion criteria, and the studies that did not comply with the research objectives was excluded (Figure 1).

3. Data Extraction

Data were extracted according to a form that was created before the literature search. The details of extracted studies were including the First author’s name, publication year, sample size, type of sampling, study population, aims of the publication, experimental methodology (in vivo, ex vivo, and in vitro), key finding, language, gender, age, type of study (Table 2).

3.1. Gathering, Summarizing, and Declaration of Results

Based on the extracted publications, the increasing or decreasing effects of statins/HMG-CoA reductase inhibitors such as Lovastatin, Fluvastatin, Pravastatin, Rosuvastatin, Atorvastatin, and Pitavastatin on insulin secretion of pancreatic islet cells was reported. Then the results were reported using different tables.

3.2. Quality Assessment

Two authors have independently assessed the risk of bias based on the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) risk of bias tool (27). This evaluation tool is derived from Cochrane’s Risk of Bias tool for clinical studies that applied to animal studies (28). The tool consists of 10 main questions related to selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. If the answer of questions was “yes” or “no” or “unclear”, the question was answered adequately, not answered, and not enough information to answer yes or no respectively. Then according to the received answers, the risk of bias domains was classified as low, high, or unclear.

4. Results

4.1. Search Results

At first, records identified through PubMed, Scopus, ISI, and ProQuest database searching were (n = 146274, n = 168033, n = 191668, and n = 11493 respectively. Then, 44991 studies were remaining for all mentioned databases in the screening stage. After removing full-text unavailable articles and the articles not relevant to the subject of study 78 studies were selected in the eligibility stage of searching. In the end, 20 articles that fulfilled the inclusion criteria of the present study were included and 58 studies were excluded because of the lack of information about the effect of statins on insulin secretion of islets, no concomitant referral to statins or islet or insulin secretion, and removed duplicate (Figure 1).

4.2. Study Characteristics

Ninety-five percent of the studies were articles and 5% were conference. All of the studies were original and experimental. The language of 95% of studies was English and 5% were Chinese. The year of publication of 25% of studies was conducted from 2000 to 2010 and 75% from 2011 to 2021. The population sampling of 20 studies was from mouse and rat or pancreatic islet of these animals, and 2 studies sampling were done in the pancreatic islet of humans. The gender of the administered mice in the included studies was 18.2% female, 22.7% male, and 9.1% not mentioned. This variable was 9.1% female, 18.1% male, and
The same effect was observed after in vitro atorvastatin 100 µM (24 h) (8), and 0.2, 2, and 20 µM (24 h) (26) consumption. In vivo results of rosuvastatin 2 mg/kg (12 weeks) administration in drinking water showed a reducing effect in islets insulin secretion of normal diet (ND) consumed mice, and increased this variable in the high-fat diet group (22). Moreover, rosuvastatin at the doses of 10 µM and 100 nM (24 h) (8, 24) decreased insulin secretion of pancreatic islet cells. A similar effect occurred after fluvastatin 10 (24) and 100 µM (22) was added in the medium containing islets of Langerhans for 24 h. Simvastatin 2.7 nM (24 and 48 h) (16) and 1 µM (about 200 seconds) (23) reduced the secretion of insulin from the islets. Furthermore, this antidiabetic hormone increased after 1 h administration of simvastatin 1 µM or 100 nM in the islets medium (21). However oral ingestion of pitavastatin 3 mg/kg for 16 weeks did not affect on islets insulin secretion (20), but in vitro utilization of this drug at the doses of 100 nM for 24 h decreased this factor (8). In the end, lovastatin 10 µM (24 h) reduced this hormone secretion from the islet cells of the pancreas (24).

5. Discussion

The main finding of in vivo studies revealed that pravastatin (7, 10, 14, 15, 17-19), and rosuvastatin (22) could increase and decrease islets insulin secretion or concentration, while atorvastatin (11, 24) and fluvastatin (11) just reduced this variable and pitavastatin had no effect on it (20). The results of in vitro studies showed that pravastatin and induced both increasing (10) and decreasing (8, 17) effects on insulin secretion from the pancreatic islet cells. In addition, administration of atorvastatin (8, 11-13, 16, 24-26), rosu-
vastatin (8, 24), fluvasatatin (11, 12, 24), pitavastatin (8), simvastatin (16, 23), and lovastatin (24) decreased islet insulin secretion in the medium.

Abe et al. revealed that the uptake of pravastatin into β-cell through organic anion transporting polypeptides (oatp) is the main reason for increased islet insulin secretion, and the evidence showed oatp3 mediate this transporting (10). However, previous studies elucidated that both oatp1 and oatp2 contributed to this drug membrane transporting (29, 30). The results of Huang et al. study demonstrated a similar effect on the islets insulin secretion and serum insulin level, and the main expressed mechanisms of this event were an increase in the islet blood flow (15). This alteration was occurred via the increase of antithrombotic and anti-inflammatory effects of this statin that induce endothelium-dependent vasodilation (7, 14). In contrast with Abe et al. and Huang et al. studies, Lorza-Gil et al. showed that pravastatin induced hyperglycemia and hypoinsulinemia and decreased glucose-stimulated pancreatic islet insulin secretion (17). These effects may be related to the increased lipid peroxidation and overproduction of free radicals such as hydrogen peroxide (H₂O₂) which leads to islet oxidative stress damage including impaired insulin signaling, proteolysis, apopto-
sis, and cell death (18, 19). Consequently, chronic exposure to pravastatin reduced the production of coenzyme Q10 (CoQ10) is a major intracellular antioxidant in the liver and this alteration can induce oxidative stress in the pancreatic islets. Therefore, in vivo, ex vivo, and in vitro utilization of CoQ10 supplementation improved statin-induced hyperglycemia, insulin resistance, glucose-stimulated insulin secretion (GSIS), and β-cell apoptosis through the elimination of oxidative stress (17).

Shen et al. showed that chronic treatment of high-fat diet (HFD) mice with atorvastatin, lovastatin, rosuvastatin, and fluvastatin decreased β-cell mass and size, quantities of mature insulin granules, and impaired glucose-induced insulin secretion (GIIS). Atorvastatin induced these disorders via the impairment of isoprenoid production, the expression of small G proteins, and the mechanistic target of rapamycin (mTOR) signaling as key pancreatic transcription factors (TFs). Moreover, Geranylgeranyl pyrophosphate supplementation recovered these alterations and improved the negative effects of atorvastatin on β-cell function (24). Urbano et al. confirmed that administration of atorvastatin as a lipophilic statin inhibits GIIS in pancreatic human islets and rat insulin-secreting cells (INS-1), and this effect was related to the mitochondrial dysfunctions induced by oxidative stress, reactive oxygen species (ROS) overproduction, and suppressed CoQ10 as an antioxidant produced by the liver (25). Moreover, the islets incubation with atorvastatin and fluvastatin 100 µM indicated a significant decrease in ATP content and GSIS. Therefore, these statins may inhibit GSIS via reducing ATP content and strength of their lipophilicity in the islet of Langerhans (12). Chenodeoxycholic acid (CDC), as a bile acid, can increase insulin secretion through elevation of Intracellular Ca²⁺ and farnesoid X receptor (FXR) as a member of the nuclear receptor superfamily with an important activity in the lipid and glucose metabolism. It was reported that atorvastatin reduced GSIS without affecting ATP synthesis in cultured islets. This effect was occurred by inhibition of CDC and FXR activities in the β-cell. Finally, these disorders may play a key role in the progression of diabetes mellitus (13, 31). Free fatty acid receptor 1 (FFA1) participates in the GSIS, and atorvastatin diminished potassium-stimulated insulin secretion through inhibition of FFA1 and pancreatic and duodenal homeobox 1 (PDX-1) in INS-1 cells. Hence, FFA1 regulates the atorvastatin-induced pancreatic β-cell dysfunction and pioglitazone improved this disorder by the increase of FFA1 expression (26).

Human pancreatic β-cells exposure to 100 nM statins including atorvastatin, pravastatin, rosuvastatin, and pitavastatin decreased cell viability, rate of insulin secretion, and GIIS (28 mM). Also, atorvastatin and pravastatin reduced glucose transporter 2 (GLUT-2) expressions, and atorvastatin, pravastatin, and rosuvastatin inhibited GLUT-4 levels in human skeletal muscle cells (HSkMC). Therefore, statins in addition to pancreatic β-cells damage, Statins can induce insulin resistance in HSkMC. However, 100 nM of mentioned statins induced β-cells dysfunction, but these effects were not observed at doses of 10 and 1 nM (8). Beltowski et al. showed that atorvastatin or fluvastatin reduced GSIS during in vivo and ex vivo situations. The production of signaling endoge-
Table 3. Characteristics of Article

| Characteristics of Article     | No. (%) |
|-------------------------------|---------|
| **Content type of studies**   |         |
| Article                       | 19 (25) |
| Conference                    | 1 (5)   |
| **Type of article**           |         |
| Original research and experimental study | 20 (100) |
| **Year of publication**       |         |
| 2000 - 2010                   | 5 (25)  |
| 2011 - 2021                   | 15 (75) |
| **Population**                |         |
| Animal                        |         |
| Mouse or Islet cell of mouse  |         |
| Female                        | 4 (18.2)|
| Male                          | 5 (22.7)|
| Not mentioned                 | 2 (9.1) |
| Rat or Islet cell of rat      |         |
| Female                        | 2 (9.1) |
| Male                          | 4 (18.1)|
| Not mentioned                 | 3 (13.7)|
| Human                         |         |
| Gender                        |         |
| Not mentioned                 | 2 (9.1) |
| **Sample size**               |         |
| ≤ 50                          | 12 (60) |
| > 50                          | 4 (20)  |
| Not mentioned                 | 4 (20)  |
| **Average of age**            |         |
| Human                         |         |
| Not mentioned                 | 1 (5)   |
| Animal                        |         |
| Under 2 months                | 8 (40)  |
| Over 2 months                 | 2 (10)  |
| Not mentioned                 | 9 (45)  |
| **Type of sampling**          |         |
| Random sampling               | 20 (100)|

Nous hydrogen sulfide (H2S) that inhibits islets insulin secretion can be affected by statins. Hydrogen sulfide (H2S) production was more in the rats’ islets of Langerhans that received atorvastatin or fluvastatin. Hence, these statins inhibit GIIIS via augmenting H2S signaling in the isolated islets (11).

Rosuvastatin administration showed two different effects in HFD and ND mice. This statin reduced insulin content in ND and HFD mice, while the insulin secretion process amplifies in HFD ingested group. Also, deleterious effects such as impaired β-cell function, decreased insulin content, disturbed Ca²⁺ signaling were observed in long-term consumption of rosuvastatin. Thus, this drug can accelerate the risk of new-onset diabetes through a negative effect on β-cells (22).

As revealed in Mizukami et al. study, Pitavastatin treatment did not increase islet insulin content in normal GK and Wistar rats. However, this statin suppressed hepatic lipid contents, islet fibrosis, and macrophage migration in HFD rats, but these effects did not improve insulin content in these animals. Since there are no significant differences between Wistar rats consuming HFD + pitavastatin and Wistar rats consuming HFD in figure 8 of Mizukami et al. study, it seems that the increase in islets’ insulin content refers to the HFD in order to pitavastatin (20).

In one ex vivo study, simvastatin impaired insulin secretion from the islet of Langerhans reversibly and rapidly. The mechanism of this effect remained unknown because simvastatin had no effect on intracellular Ca²⁺ concentration and it was suggested that decrease insulin granule trafficking may produce this impairment action (23). However, it was revealed that statins reduced insulin secretion in HIT cells as a hamster β-cell line, but Ishikawa et al. showed supraphysiological concentrations of statins such as simvastatin and atorvastatin could inhibit islets insulin secretion, and this event recommended that treating doses of statins administered in hypercholesteremic patients have not deteriorated effects on insulin action (16).

5.1. Conclusions

In conclusion, in vivo studies assessment of pravastatin and rosuvastatin showed both drugs increase and decrease islets insulin secretion, and atorvastatin and fluvastatin reduced this variable. In vitro articles indicated that all statin drugs that investigated in the present study reduced this hormone secretion except pravastatin. Moreover, the mechanisms of increase in insulin secretion of pancreatic islets were oatps upregulation, increase blood flow of islets, and distribution in Ca²⁺ signaling. On the other hand the influenced mechanisms on decrease of insulin secretion were the adverse effect in Ca²⁺ signaling, induced oxidative stress in islet, reduced CoQ10 production, impairment of isoprenoid, inhibition of CDC and FXR functions, inhibition of FFA1, reduced GLUT-2 expressions, enhanced augmenting H2S signaling, decreased insulin granule trafficking, impaired β-cell function, and stimulated this cell apoptosis. Therefore, Pravastatin could enhance pancreatic islet insulin secretion while other statins reduced this variable. Finally, the contradictory effect of
### Table 4. The Properties of Statins Administration in the Eligible and Remained Studies

| No. | Author                      | Year | Drug’s Name | Dose       | Duration | Times of Administration | Type of Prescription | Effect on Insulin Secretion |
|-----|-----------------------------|------|-------------|------------|----------|-------------------------|----------------------|----------------------------|
| 1   | Abe et al. (10)             | 2010 | Pravastatin | 200 mg/kg  | 4 weeks  | Daily                   | Oral                 | Increase                   |
|     |                             |      |             | 100 µM     | 48 hours | Once                    | Medium               |                            |
| 2   | Beltowski et al. (16)       | 2014 | Pravastatin | Not mentioned | 1 week | Daily                   | Oral                 | No effect                   |
|     |                             |      | Rosuvastatin |            |          | Once                    | Medium               |                            |
|     |                             |      | Atorvastatin |            |          |                         |                     |                            |
|     |                             |      | Fluvastatin |            |          |                         |                     |                            |
| 3   | Chang et al. (12)           | 2011 | Atorvastatin | 100 µM    | 24 hours | Once                    | Medium               | Decrease                   |
|     |                             |      | Pravastatin |            |          |                         |                     |                            |
| 4   | Hoffmeister et al. (55)     | 2020 | Atorvastatin | 10 µM     | 24 hours | Once                    | Medium               | Decrease                   |
|     |                             |      | Fluvastatin |            |          |                         |                     |                            |
| 5   | Huang et al. (7)            | 2008 | Pravastatin | 0.5 mg/kg  | 10 seconds | Once                   | Intravenous          | Increase                   |
| 6   | Huang et al. (14)           | 2006 | Pravastatin |            |          |                         |                     |                            |
| 7   | Huang et al. (15)           | 2011 | Pravastatin | 100 µM    | 24 hours | Once                    | Medium               | Decrease                   |
|     |                             |      | Rosuvastatin |            |          |                         |                     |                            |
|     |                             |      | Atorvastatin |            |          |                         |                     |                            |
|     |                             |      | Fluvastatin |            |          |                         |                     |                            |
| 8   | Ishikawa et al. (16)        | 2011 | Pravastatin | 8.1 nM     | 24 hours | Once                    | Medium               | No effect                   |
|     |                             |      | Rosuvastatin | 7.1 nM    | 40 hours |                         | Oral                 | Decrease                   |
| 9   | Lorza-Gil et al. (17)       | 2019 | Pravastatin | 400 mg/L  | 1 month  | Drinking water          | Oral                 | Decrease                   |
|     |                             |      | Rosuvastatin | 70 µM     | 40 hours |                         |                     |                            |
| 10  | Lorza-Gil et al. (18)       | 2006 | Pravastatin | 400 mg/L  | 3 months | Drinking water          | Oral                 | Decrease                   |
|     |                             |      | Rosuvastatin | 400 mg/L  | 3 months | Drinking water          | Oral                 | Decrease                   |
| 11  | Minakami et al. (20)        | 2011 | Pravastatin | 3 mg/kg   | 16 weeks | Daily                   | Oral                 | No effect                   |
| 12  | Real et al. (21)            | 2014 | Simvastatin | 1 µM      | 1 hour   | Once                    | Medium               | No effect                   |
|     |                             |      | Pravastatin | 100 nM    | 24 hours |                         | Oral                 | Increase in HFD; Decrease in ND |
| 13  | Scantin et al. (22)         | 2016 | Rosuvastatin | 0.2 mg/kg | 12 weeks | Drinking water          | Oral                 | Increase in HFD; Decrease in ND |
|     |                             |      |             |           |          |                         |                     |                            |
| 14  | Shen et al. (14)            | 2019 | Simvastatin | 1 µM      | 10 seconds | Once                   | Medium               | Decrease                   |
|     |                             |      | Pravastatin | 100 nM    | 24 hours |                         | Oral                 | No effect                   |
| 15  | Takei et al. (5)            | 2020 | Floxed HMGCR | Not mentioned |      |                         |                     |                            |
| 16  | Ubano et al. (25)           | 2007 | Rosuvastatin | 10 mg/mL  | 24 hours |                         | Oral                 | No effect                   |
|     |                             |      | Pravastatin | 100 mg/mL | 40 hours |                         |                     |                            |
| 17  | Zhao et al. (14)            | 2015 | Rosuvastatin | 100 nM    | 24 hours |                         | Oral                 | Decrease                   |
|     |                             |      | Atorvastatin | 10 µM     | 24 hours |                         | Medium               |                            |
| 18  | Zhu et al. (16)             | 2019 | Rosuvastatin | 0.2 µM, 2 µM, 10 | 24 hours |                         | Medium               | Decrease                   |
|     |                             |      | Pravastatin | µM        |          |                         |                     |                            |

**Abbreviation:** HFD, high fat diet; ND, normal diet; HMGCR, 3-Hydroxy-3-methylglutaryl-coenzyme A reductase.

**Footnotes**

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Statins on islets’ insulin secretion can indicate the existence of laboratory and clinical research in this regard.

**Supplementary Material**

Supplementary material(s) is available here [To read supplementary materials, please refer to the journal website and open PDF/HTML].

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GANIC ANION TRANSPORTER SUBTYPE (OATP1) THAT TRANSPORTS THYROID HORMONES AND TAUCRCHOLATE AND COMPARISON WITH OATP2. J Biol Chem. 1998;273(35):22395-401. doi: 10.1074/jbc.273.35.22395. [PubMed: 9712861].

31. Claudel T, Staels B, Kuipers F. The Farnesoid X receptor: a molecular link between bile acid and lipid and glucose metabolism. Arterioscler Thromb Vasc Biol. 2005;25(10):2020-30. doi: 10.1161/01.ATV.0000178994.21828.a7. [PubMed: 16037564].
| No. | Author               | Publication Year | Sample Size | Study Population | Aims                                                                 | Experimental Methodology | Key Finding                                                                 | Language | Gender | Age | Type of Sample | Type of Study |
|-----|---------------------|-----------------|-------------|-----------------|----------------------------------------------------------------------|--------------------------|-------------------------------------------------------------------------------|----------|--------|----|----------------|--------------|
| 1   | Abe et al. (16)     | 2010            | 24          | Mouse & Islet   | 1. Examine the transport of pravastatin into the islets or the effect of this drug on insulin secretion. | In vitro                 | I. The uptake of pravastatin into β-cells via organic anion transporters contributes to insulin secretion. | English   | Male   | 6  | Random         | Original article |
| 2   | Bellowski et al. (6) | 2018            | Not mentioned | Rat & Islet cell | 2. Assessment of the effect of statins on insulin secretion and the underlying mechanism. | In vitro & ex vivo       | I. Lipophilic statins inhibit glucose-induced insulin secretion by augmenting H-25 signaling in pancreatic islets. 2. The effect is mediated by statin-induced CoQ depletion and may contribute to detrimental effects of statins on glucose homeostasis. | English   | Male   | Not mentioned | Random | Congress |
| 3   | Chang et al. (14)    | 2010            | Not mentioned | Islet cell of Rat | 3. Evaluation of the inhibitory effect of angiotensin antagonist on pancreatic islet blood flow, insulin levels and glycemia in an animal model of type 2 diabetes. | In vitro                 | I. Atorvastatin and fluvastatin may inhibit GSIS by decreasing ATP content in pancreatic islets. 2. This inhibitory effect is related to the strength of its lipophilic property. | English   | Not mentioned | Not mentioned | Random | Original article |
| 4   | Hoffmann et al. (13) | 2020            | Not mentioned | Islet cell of Mouse | 4. Investigation of the role of statins in glucose-stimulated insulin secretion. | In vitro                 | I. The diabetogenic risk of statins is coupled to the activity of common II (II) dependent signaling pathways in β-cells. 2. Statins abolish the insulinotropic effect of β-adrenergic agonists. 3. FOX6 determines the level of impairment of β-cell function by the statins. | English   | Male & Female | 6–12 months | Random | Original article |
| 5   | Huang et al. (18)    | 2006            | 32          | Rat             | 5. Statins induction insulin secretion in vivo in rats through effects on β-cell blood perfusion. | In vitro                 | I. The anti-diabetic actions of statins and other RAS inhibitors might act in part through the beneficial direct effect on β-cell insulin secretion. | English   | Male   | Not mentioned | Random | Original article |
| 6   | Huang et al. (15)    | 2007            | 32          | Rat             | 6. Investigation of the role of statins in glucose-stimulated insulin secretion. | In vitro                 | I. Atorvastatin and fluvastatin may inhibit GSIS by decreasing ATP content in pancreatic islets. 2. This inhibitory effect is related to the strength of its lipophilic property. | English   | Male & Female | Not mentioned | Random | Original article |
| 7   | Huang et al. (12)    | 2009            | 50          | Rat             | 7. Investigation of the gender-specific effects of ACE inhibition, AngII receptor antagonism, statin treatment and palmitic acid administration on pancreatic β-cell function and viability. | In vitro                 | I. Atorvastatin and fluvastatin may inhibit GSIS by decreasing ATP content in pancreatic islets. 2. This inhibitory effect is related to the strength of its lipophilic property. | English   | Male & Female | Not mentioned | Random | Original article |
| 8   | Ibellou et al. (14)  | 2005            | 48          | Islet cell of Mouse | 8. Investigation of the role of statins in glucose-stimulated insulin secretion. | In vitro                 | I. Atorvastatin and fluvastatin may inhibit GSIS by decreasing ATP content in pancreatic islets. 2. This inhibitory effect is related to the strength of its lipophilic property. | English   | Male & Female | Not mentioned | Random | Original article |
| 9   | Lotto-Gil et al. (23) | 2019            | 32          | Mouse & Islet cell | 9. Investigation of the role of statins in glucose-stimulated insulin secretion. | In vitro & ex vivo       | I. Atorvastatin and fluvastatin may inhibit GSIS by decreasing ATP content in pancreatic islets. 2. This inhibitory effect is related to the strength of its lipophilic property. | English   | Female | 4 weeks | Random | Original article |
| 10  | Lotto-Gil et al. (20) | 2019            | 36          | Mouse & Islet cell | 10. Investigation of the role of statins in glucose-stimulated insulin secretion. | In vitro & ex vivo       | I. Atorvastatin and fluvastatin may inhibit GSIS by decreasing ATP content in pancreatic islets. 2. This inhibitory effect is related to the strength of its lipophilic property. | English   | Female | 4 weeks | Random | Original article |
| 11  | Lotto-Gil et al. (22) | 2016            | 20          | Mouse & Islet cell | 11. Investigation of the role of statins in glucose-stimulated insulin secretion. | In vitro & ex vivo       | I. Atorvastatin and fluvastatin may inhibit GSIS by decreasing ATP content in pancreatic islets. 2. This inhibitory effect is related to the strength of its lipophilic property. | English   | Female | 4 weeks | Random | Original article |
| 12  | Minourik et al. (27) | 2012            | 12          | Rat             | 12. Investigation of the role of statins in glucose-stimulated insulin secretion. | In vitro                 | I. Atorvastatin and fluvastatin may inhibit GSIS by decreasing ATP content in pancreatic islets. 2. This inhibitory effect is related to the strength of its lipophilic property. | English   | Male   | 6 weeks | Random | Original article |

**Table 2. The Characteristics of Eligible and Remained Studies**
| Study | Year | Species | Cell Type | In Vivo | In Vitro | Gender | Age | Duration | Publication Details |
|-------|------|---------|-----------|---------|---------|--------|-----|----------|-------------------|
| 1     | 2018 | Mouse   | Islet     | In vitro| In vitro| Male   | 3-6| Random   | English Male 3-6 months Random Original article |
| 2     | 2016 | Mouse   | Islet     | In vitro| In vitro| Female | 8   | Random   | English Female 8 weeks Random Original article |
| 3     | 2020 | Mouse   | Islet     | In vitro| In vitro| Not mentioned | Not mentioned | Random | Original article |
| 4     | 2020 | Mouse   | Islet     | In vitro| In vitro| Male   | 8   | Random   | Original article |
| 5     | 2020 | Human   | Human & Rat| In vitro| In vitro| Male   | 5 weeks | Random | Original article |
| 6     | 2020 | Human   | Human & Rat| In vitro| In vitro| Not mentioned | Not mentioned | Random | Original article |
| 7     | 2005 | Human   | Islet     | In vitro| In vitro| Male   | Not mentioned | Not mentioned | Original article |
| 8     | 2009 | Human   | Islet     | In vitro| In vitro| Not mentioned | Not mentioned | Original article |

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