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Evaluating the Efficacy of Pharmacological Therapy for Prader-Willi Syndrome: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Prader-Willi Syndrome (PWS) is a rare genetic disorder. To improve the health deterioration of PWS, investigating optimal treatment options for PWS is required. Thus, we aimed to evaluate the efficacy of pharmacotherapies compared with supportive care or placebos in patients with PWS. **Methods:** PubMed and EMBASE databases were used to search for randomized controlled trials (RCTs) evaluating the efficacy of pharmacotherapy in PWS patients. Only RCTs that evaluating the efficacy of pharmacotherapy in PWS patients were retrieved. **Results:** A total of 26 studies were included to evaluate body composition, hormones, glucose levels and hyperphagia behavioral status. Pharmacological treatment group showed a significant decrease of body fat (mean difference (MD): -6.32, 95% confidence interval (CI): -10.58 to -2.06, p=0.004), a significant increase of lean body mass (LBM) (MD: 1.86, 95% CI: 1.43 to 2.30, p<0.00001) and insulin-like growth factor 1 (IGF-1) levels (MD: 241.62, 95% CI: 68.59 to 414.64, p=0.006) compared with the control group. Nevertheless, based on other outcomes evaluated by the current systematic review, pharmacological options showed different efficacy in treating PWS. **Conclusion:** Pharmacological therapies were effective to decrease significantly in body fat and increase significantly on LBM and IGF-1 levels in patients with PWS. However, still, individualized therapies should be considered in real-world practice in PWS treatment.

KEYWORDS: Prader-Willi syndrome, pharmacological therapy, systematic review, meta-analysis, efficacy

Prader-Willi Syndrome (PWS) is a rare genetic disability with a prevalence rate of 1 in 10,000-30,000 live births.[1,2] PWS is a complex developmental disability caused by a deficiency of genes expressed on chromosomes 15q11-q13,[3,4] resulting in growth hormone (GH) deficiency, hypogonadism, reproductive dysfunction, behavioral problems, hyperphagic problems, and obesity.[5,6] The cause of the abnormal body composition in PWS is not completely known. However, a unique pattern of body composition with increased body mass index (BMI) or total body fat mass (FM) and a decrease in lean body mass (LBM) has been observed in patients with PWS.[7] Individuals with PWS may have pathological obesity resulting from excessive weight gain or severe hyperphagia.[8] Physical deterioration and weight gain in patients with PWS can cause negative consequences such as metabolic dysfunction, cardiovascular disease, and early death.[8]

There are pharmacological and non-pharmacological methods for treating these complications in patients with PWS. Non-pharmacological methods, such as dietary restriction or bariatric surgery, have limitations in improving the condition of patients with PWS.[8] In contrast, although they are non-pharmacological treatments, dietary interventions have been reported to be effective in preventing excessive weight gain.[9] However, another study has reported that nutritional intervention

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does not contribute significantly to weight loss.[10] Especially in patients with PWS, food restriction was not associated with appetite reduction or the patient's ability to live independently because they needed help from their families.[11] Although non-pharmacological treatments for PWS have been ineffective, the efficacy of pharmacological treatment for PWS is supported by various studies. There is currently no standard therapy for treating PWS. In addition, there is limited evidence to prove the efficacy of pharmacological options. Hence, an evaluation of the benefits of pharmacological treatment in patients with PWS is needed.[8]

In previous systematic reviews and meta-analysis, the effects of pharmacological treatments on body composition variables such as height, BMI, and FM have evaluated.[12-15] As a result of previous meta-analysis, increased LBM and decreased FM were consistently observed.[12-15] Since previous studies have investigated randomized controlled trials (RCTs) and non-randomized controlled trials (NRCTs) simultaneously,[12-15] biases were unpreventable. Moreover, there are additional studies that have been investigated the efficacy of pharmacological treatment in PWS patients but are not included in the previous meta-analysis. These studies need to be included in the analysis.

Hence, the current meta-analysis aimed to assess the efficacy of pharmacological therapies compared to supportive care or placebos in PWS patients with RCTs.

Methods

The current meta-analysis was reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PRISMA checklist was indicated in Supplementary Table 1. The study protocol was registered in the International Prospective Register of Systematic Reviews database with registration number: CRD42022320845.

Search Strategy

PubMed and EMBASE databases were used for searching relevant studies published before 18 March 2022. The search was conducted using the keywords combined with "PWS", "pharmacological treatment", and relevant Medical Subject Headings (MeSH) terms. The detailed search strategy was indicated in Supplementary Table 2 and Supplementary Table 3. The search strategy was targeted at published studies that estimated the efficacy of pharmacological treatments for PWS and was limited to full-text articles written in English. In order to limit to retrieve only full-text English articles, the three investigators manually reviewed the articles. References in the collected articles and systematic reviews were manually browsed to identify additional studies.

Study Selection

Three independent investigators assessed the titles and abstracts of the retrieved articles to identify potentially related articles. This review included (1) all RCTs that registered patients with PWS to evaluate the efficacy of pharmacological treatments and (2) studies that providing outcomes of body composition, hormones, and glucose levels, and hyperphagic status in patients with PWS. We excluded the studies following four reasons: (1) inappropriate outcome measure, (2) non-pharmacological intervention, (3) full-text records not retrieved and (4) not placebo or untreated controls. All disagreements between the three investigators were resolved through discussion.

Outcomes

Changes in body composition parameters, such as LBM, FM, body fat percentage, BMI, weight, and height were assessed. In addition, changes in glucose levels and hormones such as insulin, insulin-like growth factor binding protein 3 (IGFBP-3), insulin-like growth factor 1 (IGF-1), glucose and adiponectin levels were evaluated. Additionally, the hyperphagic status was assessed.

Data Extraction and Quality Assessment

Data extracted from the retrieved studies included sample size, intervention, type of control group, study design, registration number, study period, body composition, hormone & glucose levels and hyperphagia behavior. Three investigators performed data extraction and assessment of internal study validity and quality. The risk of bias assessment tool developed by the Cochrane Collaboration was used to evaluate quality of RCTs.[16] The evidence for the included study was assessed as a Grading of Recommendations, Assessment, Development and Evaluations profiler (GRADEpro) approach; classified as high, moderate, low, or very low.[17] All disagreements between the three investigators were resolved through discussions.

Data Synthesis and Analysis

We determined the overall changes in body composition,

hormone, glucose levels and hyperphagic status after pharmacological treatment. We extracted the change of the measurements. In the case of articles that show only baseline and final levels, the change was calculated through those levels. Net changes were quantified as differences between baseline and final measures. We assumed a correlation of r= 0.5 to calculate the standard deviation (SD) of the change. To perform meta-analysis on several studies, only studies in which the level of each outcome expressed as mean±SD were analyzed. Hence, we excluded the studies that each outcome level expressed as median with range or interquartile range in meta-analysis. The overall effect size for the studies represented as the mean difference (MD) and 95% confidence interval (CI). We equalized the units for each outcome to analyze with MD and used them as follows; BMI (kg/m^2), LBM (kg), body fat (%), weight (kg), IGF-1 (ng/mL) and fasting insulin (mIU/L). Since other outcomes did not have enough number of articles to analyze with mean±SD, meta-analysis performed on only these six outcomes. Statistical significance was set at p<0.05.

I^2 statistics were used to decide the significance of heterogeneity among studies classified as low (<25%), moderate (25-50%) or high (>50%). If I^2 <25%, meta-analysis was conducted with a fixed-effect model. Otherwise, meta-analysis was conducted with random-effect model. When I^2> 50%, sensitivity analysis was performed by omitting each study individually. Sensitivity analysis was also performed when the meta-analysis results were affected by a specific study with a large weight. Due to less than 10 studies were included in each analysis, publication bias was not evaluated. The meta-analysis was conducted using Review Manager (RevMan [Computer Program]. Version 5.4, The Cochrane Collaboration, 2020), R (version 4.2.1) and Excel.

Results

Study selection

We identified 241 potentially eligible studies extracted from PubMed and EMBASE databases (Fig. 1). Full-text screening reduced the number of studies to 90. 66 of 90 studies were excluded for the following four reasons: (1) inappropriate outcome measures (n=57), (2) non-pharmacological interventions (n=6), (3) full-text records not retrieved (n=2), and (4) not placebo or untreated controls (n=1). Two more articles were identified through a nonautomatic search of the reference lists of the retrieved studies. Ultimately, 26 studies were included in qualitative analysis.[18-43] and 11 of them were included in quantitative analysis.[18,20,22,25,26,30,32,37-40]

Study characteristics

The basic characteristics of the total 26 studies were presented in Table 1.[18-43] Body composition was evaluated in 21 studies,[18-22,24-26,28,30,32-33,35-43] hormone and glucose levels were evaluated in 21 studies[18,19,21-25,29-31,33-43] and status of hyperphagic behavior was evaluated in three studies.[20,22,27] Most of the 26 studies used GH administration[18,29-43] and 10 studies used the administration of additional drugs including [19-28]: anticonvulsant,[20] selective methionine aminopeptidase 2 inhibitor,[21] unacylated ghrelin analog,[22] glucagon-like peptide 1 receptor agonist,[23] cannabinoid receptor CB1 inverse agonist,[24] somatostatin receptor agonist,[25] oxytocin,[19,27,28] and serotonin releasing agent.[26]

Body composition

The effects of pharmacological treatment on body composition including BMI, LBM, FM, body fat, weight and height were summarized in Table 2.[18-22,24-26,28,30,32-33,35-43]

Thirteen studies evaluated the effects of pharmacological treatment on BMI [18-20, 24, 25, 28, 30, 32-33, 39-42]. BMI was reduced in seven studies[18,20,24,28,30,33,41] and in the other six,[19,25,32,39-40,42] it was either unchanged or slightly increased (Table 2). In the case of using GH, BMI showed inconsistent results because it was unchanged,[42] increased[32,39,40] or decreased.[18,30,33,41] Similarly, in the case of using non-GHs such as oxytocin showed an inconsistent tendency with an increased BMI in one study[19] and a decreased BMI in another study.[28] Otherwise, BMI tended to decrease in non-GH treatments such as anticonvulsants[20] and cannabinoid receptor CB1 inverse agonist[24] except for an increase in somatostatin receptor agonist.[25] Of the 13 studies,[18-20,24,25,28,30,32-33,39-42] only six studies which BMI were expressed in mean±SD were analyzed.[18,20,25,30,32,40] Patients who received pharmacological treatment showed a nonsignificant decrease in BMI compared to the control group (MD: −0.73, 95% CI: −1.95 to 0.50, p=0.25) (Fig. 2a). We performed a sensitivity analysis because of the large weight of De Waele et al. (2008), but there was no difference in I^2.

The effects of pharmacological treatment on LBM were evaluated in ten studies.[18,19,21,30,32,35,38-40,42] Except for one study,[21] the LBM increased in nine studies (Table 2).[18,19,30,

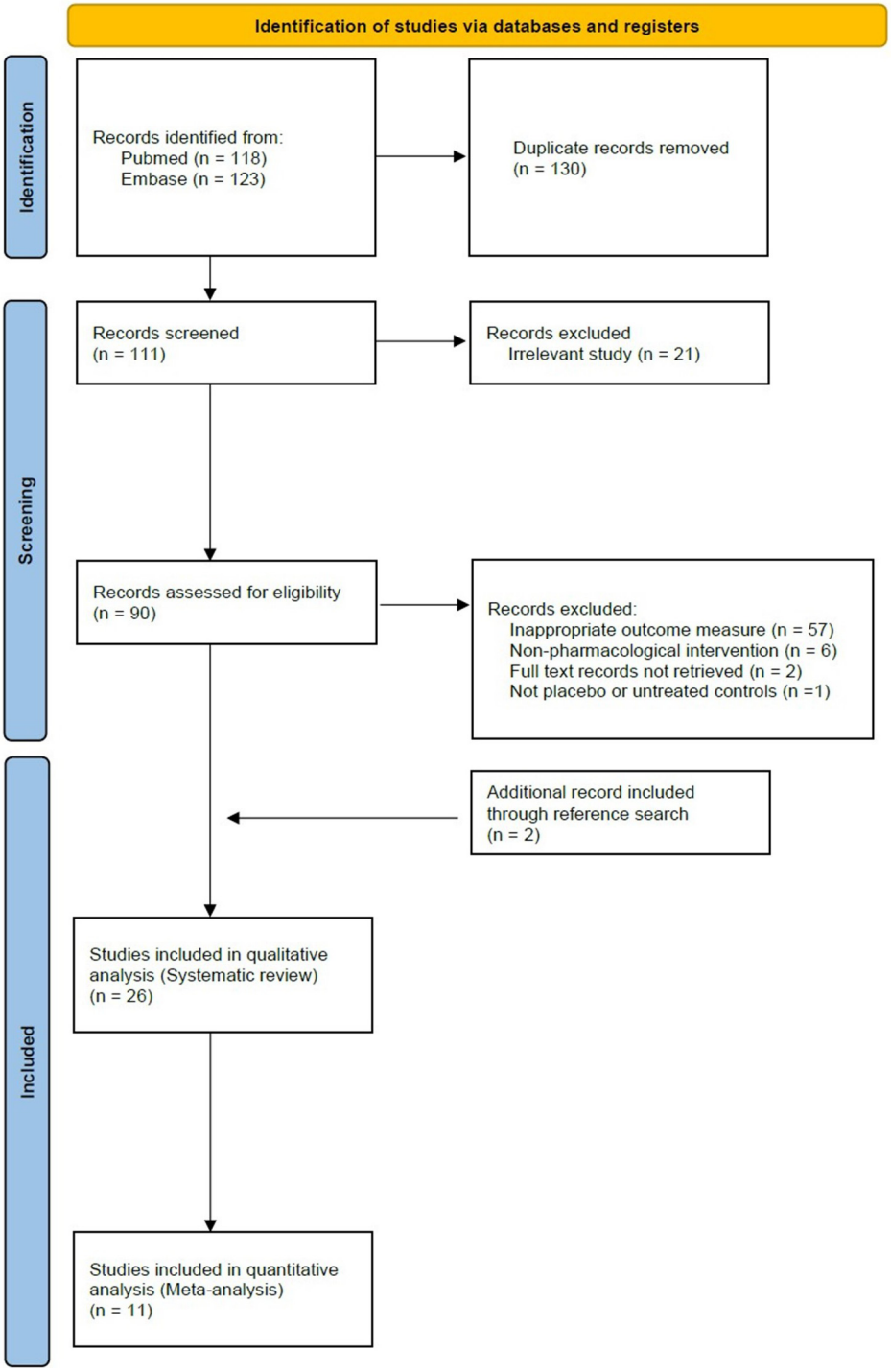

Fig. 1. The flowchart of the study selection process for the systematic review and meta-analysis.

[32,35,38-40,42] LBM increased in all studies that using GH.[18,30,32,35,38-40,42] A study that using oxytocin, one of the non-GH treatments, also showed an increase in LBM.[19] In contrast, LBM decreased when selective methionine aminopeptidase 2 inhibitor, another type of non-GH treatments, was used.[21] Of the ten studies,[18,19,21,30,32,35,38-40,42] only six studies which LBM were expressed in mean±SD were analyzed[18,30,32,38-40] Patients who received pharmacological treatment showed a significant improvement in LBM compared to the control group (MD: 1.86, 95% CI: 1.43 to 2.30, p<0.00001) (Fig. 2b).

Table 1. Characteristics of included studies

Study name	Patient	Intervention	Comparator	Registration number	Research period	Patients age
GH						
Sode-Carlsen et al. (2010) [42]	46	GH	Placebo	N/A	1 year	16-50 years
Festen et al. (2007) [41]	20	GH (Genotropin) SC 1 mg/m^2/day	Untreated	N/A	2 years	4-9 years
Bakker et al. (2015) [35]	47	GH (Genotropin) 0.035 mg/kg/day	Untreated	ISRCTN 49726762 /NTR 628	2 years	6 month-14 years
Kuppens et al. (2016 a) [40]	27	GH (Genotropin) SC 0.67 mg/m^2/day	Placebo	NTR1038	2 years	17.2 (1.8) years [a]
Myers et al. (2000) [30]	54	GH (Nutropin) 1 mg/m^2/day	Untreated	N/A	2 years	4-16 years
HAQQ et al. (2003) [32]	12	GH (Genotropin) SC 0.043 mg/kg·d	Placebo SC	N/A	1 year	4.5-14.5 years
Carrel et al. (1999) [18]	54	GH (Nutropin) 1 mg/m^2/day	Untreated	N/A	1 year	4-16 years
Hoybye et al. (2004) [29]	17	GH (Genotropin) 0.8 → 1.6 IU (0.26 → 0.53 mg) daily	Placebo	N/A	18 months	17-32 years
Hauffa et al. (1997) [34]	17	GH SC 0.15 IU/kg/day	Untreated	N/A	1 year	3-12 years
Hoybye et al. (2003 a) [39]	17	GH (Genotropin) SC 0.8 → 1.6 IU (0.26 → 0.53 mg) daily	Placebo	N/A	18 months (Placebo-controlled period: 6 months, Open label GH period: 1 year)	17-37 years
Hoybye et al. (2003 b) [31]	17	GH (Genotropin) SC 0.8 → 1.6 IU (0.26 → 0.53 mg) daily	Placebo	N/A	18 months (Placebo-controlled period: 6 months, Open label GH period: 1 year)	17-32 years
De Lind van Wijngaarden et al. (2010) [43]	85	GH (Genotropin) SC 1.0 mg/m^2/day	Untreated	N/A	2 years	6 month-14 years
Carrel et al. (2004) [38]	29	GH (Genotropin) 1 mg/m^2/day	Untreated	N/A	1 year	4-37 months
Lindgren et al. (1998) [37]	29	GH (Genotropin) SC 0.1 IU/kg/day	Untreated	N/A	1 year	3-12 years
Lindgren et al. (1999) [36]	19	GH (Genotropin) SC 0.1 - 0.2 IU/kg/day	Untreated	N/A	2 years	3.8-12.7 years
Festen et al. (2008) [33]	91	GH (Genotropin) SC 1 mg/m^2/day	Untreated	N/A	2 years	3-12 years

Table 1. Continued

Study name	Patient	Intervention	Comparator	Registration number	Research period	Patients age
Non-GH						
Anticonvulsunt						
Consoli et al. (2019) [20]	62	Topiramate 50-200 mg/day	Placebo	NCT02810483	8 weeks	12-45 years
Cannabinoid receptor CB1 inverse agonist						
Motaghedi et al. (2011) [24]	10	Rimonobant 20 mg	Placebo	N/A	6 months	19.5 - 36.3 years
Glucagon-like peptide 1 receptor agonist						
Sze et al. (2011) [23]	8	Exenatide (Byetta) SC 10 μg	Placebo SC (normal saline)	N/A	4 weeks	30.0 (2.8) years [a]
Oxytocin						
Einfeld et al. (2014) [27]	30	Intranasal oxytocin (11 participants: (13-15 years) 18 IU B.I.D, (16 years and over) 24 IU B.I.D 18 participants: (13-15 years) 32 IU B.I.D, (16 years and over) 40 IU B.I.D)	Placebo	ACTRN126090009 82213	18 weeks	12-30 years
Kuppens et al. (2016 b) [28]	25	Intranasal oxytocin (Syntocinon) twice daily (dose range: 24-48 IU/day)	Placebo	NTR4950	8 weeks	6-14 years
Damen et al. (2021) [19]	26	Intranasal oxytocin (Syntocinon) twice daily (dose range: 16-40 IU/day)	Placebo	N/A	3 months	3-11 years
Selective methionine aminopeptidase 2 inhibitor						
McCandless et al. (2017) [21]	107	Beloranib 1.8 mg or 2.4 mg	Placebo 0.45ml or 0.6ml	NCT02179151	1 year (administer 26 weeks)	12-65 years
Serotonin releasing agents						
Selikowitz et al. (1990) [26]	15	Fenfluramine capsule (5 to 7 years: 10 mg TID, 8 to 15 years: 10 mg → 20 mg TID, Over the age of 15: 20 mg TID → 40 mg TID)	Placebo capsule (lactose)	N/A	6 weeks	5.5-27 years
Somatostatin receptor agoinist						
De Waele et al. (2008) [25]	9	Octreotide (Sandostatin LAR) IM 30 mg	Placebo IM (saline)	NCT00175305	56 weeks	10.8-18.9 years
Unacylated ghrelin analog						
Allas et al. (2018) [22]	47	AZP-531 SC 3 or 4 mg	Placebo	N/A	2 weeks	18-40 years

ACTRN: Australian clinical trials registration number, AZP-531: unacylated ghrelin analog, BID: Bis In Die (=twice a day), GH: growth hormone, IM: intramuscular injection, ISRCTN: International Standard Randomised Controlled Trial Number, IU: International Unit, N/A: not available, NCT: National Clinical Trial (number), NTR: Netherlands Trial Register, SC: subcutaneous injection, TID: Ter In Die (=three times a day), [a] is indicated as Mean (Standard deviation)

Table 2. Effects of pharmacological treatments on body composition, hormone & glucose, and states of hyperphagic behavior

Study name	Body composition	Hormone & glucose	States of hyperphagic behavior
GH			
Sode-Carlsen et al. (2010) [42]	BMI (kg/m^2) unchanged LBM (kg) ↑ FM (kg) ↓	IGF-1 (ng/mL) ↑ Fasting glucose (mmol/L) unchanged Fasting insulin (pmol/L) unchanged	-
Festen et al. (2007) [41]	BMI (kg/m^2) ↓ Height (SDS) ↑	Glucose (mmol/L) ↓ Insulin (mU/L) ↑ Adiponectin (mg/L) ↑	-
Bakker et al. (2015) [35]	LBM (kg) ↑ FM (kg) ↑ Body fat (%) ↓ Height (SDS) ↑	Fasting glucose ↑ Fasting insulin ↑ Fasting adiponectin (mg/L) ↑	-
Kuppens et al. (2016 a) [40]	BMI (kg/m^2) ↑ LBM (kg) ↑ FM (kg), FM (%) ↑	Glucose (mmol/L) ↓ Insulin (pmol/L) ↓	-
Myers et al. (2000) [30]	BMI (kg/m^2) ↓ LBM (kg) ↑ Body fat (%) ↓	IGF-1 (ng/mL) ↑ Fasting insulin (mIU/L) ↑	-
Haqq et al. (2003) [32]	BMI (kg/m^2) ↑ LBM (kg) ↑ FM (kg) ↓ Body fat (%) ↓ Height (SDS) ↑	-	-
Carrel et al. (1999) [18]	BMI (kg/m^2) ↓ LBM (kg) ↑ Body fat (%) ↓ Height (SDS) ↑	IGF-1 (ng/mL) ↑ IGFBP-3 (mg/L) ↑ Fasting insulin (mIU/L) ↑	-
Hoybye et al. (2004) [29]	-	Adiponectin (mg/L) ↑	-
Hauffa et al. (1997) [34]	-	IGF-1 ↑ IGFBP-3 ↑	-
Festen et al. (2008) [33]	BMI (kg/m^2) ↓ Height (SDS) ↑	IGF-1 (ng/mL) ↑ IGFBP-3 (ng/mL) ↑	-
Carrel et al. (2004) [38]	LBM (kg) ↑ Body fat (%) ↓ Height (SDS) ↑	IGF-1 (ng/mL) ↓ Fasting insulin (mIU/L) ↑	-
Lindgren et al. (1998) [37]	Body fat (%) ↓ Height (SDS) ↑	IGF-1 (SDS) ↑ Fasting insulin (mIU/L) ↑	-
Hoybye et al. (2003 a) [39]	BMI (kg/m^2) ↑ LBM (kg) ↑ Body fat (%) ↓	IGF-1 (ng/mL) ↑ Glucose (mmol/L) ↓ Insulin (pmol/L) ↑	-
Lindgren et al. (1999) [36]	Body fat (%) ↓ Height (SDS) ↑	Insulin (mU/L) ↑	-
De Lind van Wijngaarden et al. (2010) [43]	Height (SDS) ↑	Glucose (mmol/L) ↑ Insulin (mU/L) ↑	-
Hoybye et al. (2003 b) [31]	-	IGF-1 (ng/mL) ↑ IGFBP-3 (ng/mL) ↑	-

Table 2. Continued

Study name	Body composition	Hormone & glucose	States of hyperphagic behavior
Non-GH			
Anticonvulsant			
Consoli et al. (2019) [20]	BMI (kg/m^2) ↓	-	↓
Cannabinoid receptor CB1 inverse agonist			
Motaghedi et al. (2011) [24]	BMI (kg/m^2) ↓ FM (g/cm^2) ↓ Weight (kg) ↓	IGF-1 (ng/mL) ↑ IGFBP-3 (ng/mL) ↑	-
Glucagon-like peptide 1 receptor agonist			
Sze et al. (2011) [23]	-	Fasting glucose (mmol/L) ↓ Fasting insulin (mIU/L) ↑	-
Oxytocin			
Kuppens et al. (2016 b) [28]	BMI (kg/m^2) ↓ Body fat (%) ↓ Weight (kg) ↑	-	-
Damen et al. (2021) [19]	BMI (kg/m^2) ↑ LBM (kg) ↑ Body fat (%) ↑ Weight (kg) ↑	Fasting glucose ↑ Fasting insulin ↑	-
Einfeld et al. (2014) [27]	-	-	unchanged
Selective methionine aminopeptidase 2 inhibitor			
McCandless et al. (2017) [21]	LBM (kg) ↓ FM (kg) ↓ Weight (kg) ↓	Adiponectin (mg/L) ↑	-
Serotonin releasing agent			
Selikowitz et al. (1990) [26]	Weight (kg) ↓	-	-
Somatostatin receptor agonist			
De Waele et al. (2008) [25]	BMI (kg/m^2) ↑ FM (kg) ↑ Body fat (%) ↑ Weight (kg) ↑ Height (cm) ↑	Fasting glucose (mg/dL) ↑	-
Unacylated ghrelin analog			
Allas et al. (2018) [22]	FM (%) ↓ Weight (kg) ↓	Fasting glucose (mmol/L) ↓ Fasting insulin (pmol/L) ↑	↓

BMI: body mass index, FM: fat mass, IGF-1: Insulin-like growth factor 1, IGFBP-3: Insulin-like growth factor-binding protein 3, LBM: lean body mass, mIU: milli international unit, SDS: standard deviation score, U: unit, ↑ = increased, ↓ = decreased

We conducted a sensitivity analysis because of the large weight of Carrel et al. (2004), but there was no difference in I^2.

Eight studies evaluated the effects of pharmacological treatment on FM[21,22,24,25,32,35,40,42] (Table 2). In the case of using GH, FM showed an inconsistent trend because each study showed an increased FM[35,40] or a decreased FM.[32,42] Except for somatostatin receptor agonist,[25] FM was decreased in all non-GH treatments such as selective methionine aminopeptidase 2 inhibitor,[21] cannabinoid receptor CB1 inverse agonist[24] and unacylated ghrelin analog.[22]

The effect of pharmacological treatments on body fat was

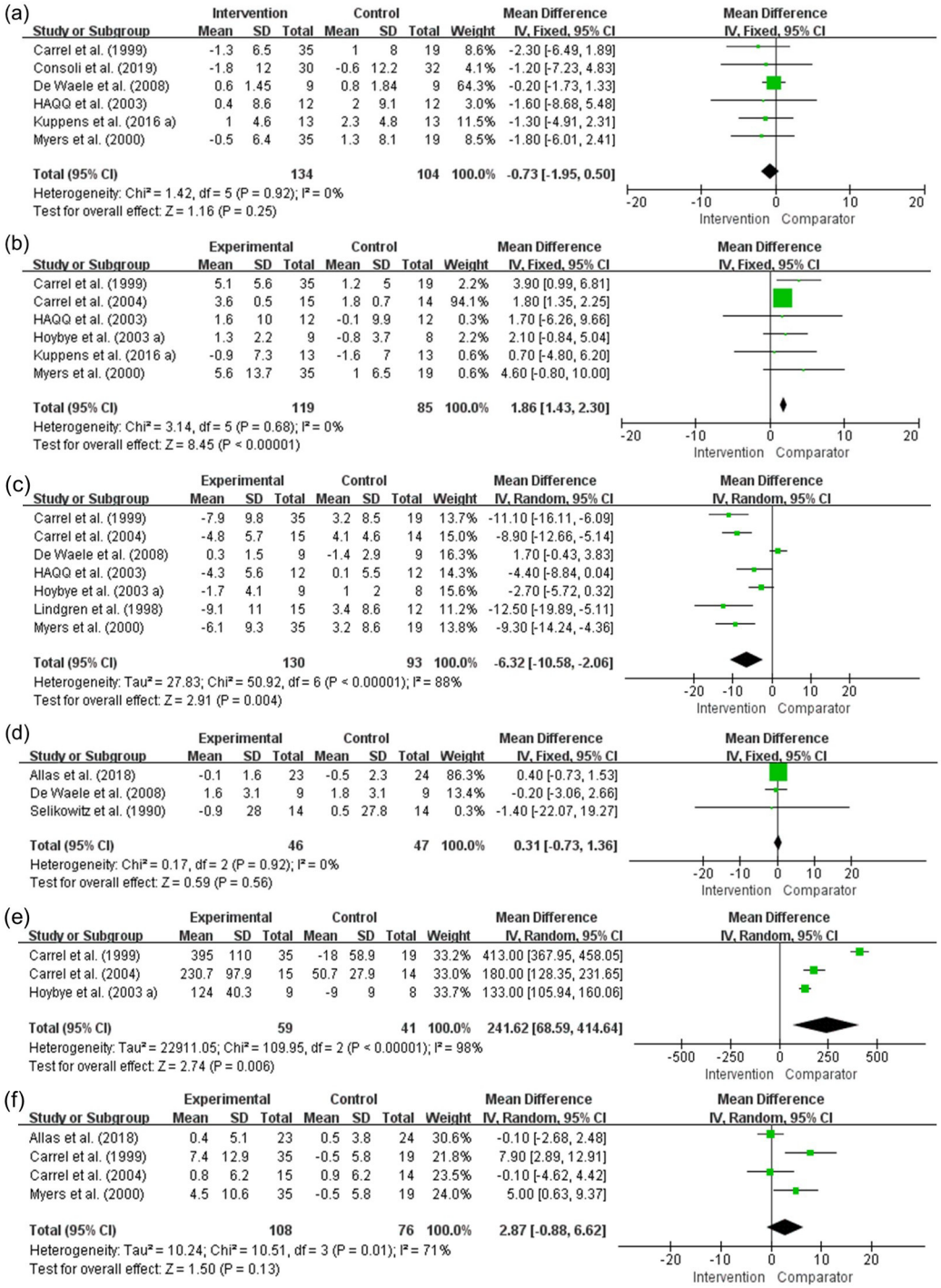

Fig. 2. Forest plots for the effects of pharmacological treatments on (a) BMI, (b) LBM, (c) body fat, (d) weight, (e) IGF-1 and (f) fasting insulin levels. Squares represent the effect size for each included studies and the size of the square represents the weight assigned to that study in the meta-analysis. Diamond indicated as meta-analyzed measure of effect. BMI: body mass index, IGF-1: Insulin-like growth factor 1, LBM: lean body mass

evaluated in 11 studies.[18,19,25,28,30,32,35-39] In nine studies, body fat was reduced,[18,28,30,32,35-39] and in the other two, it was increased[19,25] (Table 2). Body fat decreased in all studies that using GH.[18,30,32,35-39] Body fat was increased when somatostatin receptor agonist, one of non-GH treatments, was used.[25] In contrast, oxytocin, another type of non-GH treatments,

showed an increased body fat in one study[19] and a decreased body fat in another study.[28] Of the 11 studies,[18,19,25,28,30,32,35-39] only seven studies which body fat were expressed in mean±SD were analyzed.[18,25,30,32,37-39] Patients who received pharmacological treatment showed a significant decrease in body fat compared to the control group (MD: −6.32, 95% CI: −10.58 to −2.06, p=0.004) (Fig. 2c). The analyzed results may actually be heterogeneous (I^2=88%). In the case of omitting De Waele et al. (2008), I^2 decreased from 88% to 68%. De Waele et al. (2008) is the main cause of heterogeneity.

Ten studies evaluated the effects of pharmacological treatment on height[18,25,32,33,35-38,41,43] (Table 2). Increase of height was observed in all studies.[18,25,32,33,35-38,41,43] Height has increased in all studies that using GH.[18,32,33,35-38,41,43] In addition, a study that using somatostatin receptor agonist, one of non-GH treatments, also showed an increased height.[25]

In addition, the effects of pharmacological treatments on weight were evaluated in seven studies.[19,21,22,24-26,28] Weight loss was observed in four studies,[21,22,24,26] and the other three reported weight gain[19,25,28] (Table 2). Of non-GH drugs, cannabinoid receptor CB1 inverse agonist,[24] selective methionine aminopeptidase 2 inhibitor,[21] serotonin releasing agent[26] and unacylated ghrelin analog showed a decrease in weight.[22] Otherwise, in the case of using oxytocin or somatostatin receptor agonist,[19,25,28] weight was increased. Of the seven studies,[19,21,22,24-26,28] only three studies which weight were expressed in mean±SD were analyzed.[22,25,26] Patients who received pharmacological treatment showed a nonsignificant increase in weight compared with the control group (MD: 0.31, 95% CI: −0.73 to 1.36, p=0.56) (Fig. 2d). We performed sensitivity analysis due to large weight of Allas et al. (2018), but there was no difference in I^2.

Hormone & Glucose

The effects of drug treatment on hormones including IGF-1, IGFBP-3, insulin, adiponectin, and glucose levels were summarized in Table 2.[18,19,21-25,29-31,33-43]

Ten studies evaluated the effects of pharmacological treatment on IGF-1[18,24,30,31,33,34,37-39,42] (Table 2). In the case of using GH,[18,30,31,33,34,37-39,42] IGF-1 levels were increased,[18,30,31,33,34,37,39,42] except for one study.[38] Non-GH treatment such as cannabinoid receptor CB1 inverse agonist showed an increasing effect.[23] Of the 10 studies,[18,24,30,31,33,34,37-39,42] only three studies which IGF-1 levels were expressed in mean±SD were analyzed.[18,38,39] IGF-1 showed a more significant increase in the pharmacological treatment group than in the control group (MD: 241.62, 95% CI: 68.59 to 414.64, p=0.006) (Fig. 2e). The analyzed results may actually be heterogeneous (I^2=98%). In the case of omitting Carrel et al. (1999), I^2 decreased from 98% to 60%. Carrel et al. (1999) is the main cause of heterogeneity.

The effects of pharmacological treatment on IGFBP-3 were evaluated in five studies.[18,24,31,33,34] IGFBP-3 expression increased in all studies[18,24,31,33,34] (Table 2). IGFBP-3 expression with GH treatments was increased in all studies[18,31,33,34] (Table 2). The non-GH treatment cannabinoid receptor CB1 inverse agonist also showed an increase in IGFBP-3.[24]

Four studies evaluated the effects of pharmacological treatment on glucose levels.[39-41,43] Except for one study[43] glucose levels with GH treatments decreased in three studies.[39-41] In addition, the effects of pharmacological treatments on fasting glucose levels were evaluated in six studies.[19,22,23,25,35,42] In the case of using GH drugs,[35,42] fasting glucose has unchanged in one study[42] and increased in another study[35] (Table 2). In the case of using non-GH treatments,[19,22,23,25] unacylated ghrelin analog and glucagon-like peptide 1 (GLP-1) receptor agonist showed a decreasing effect.[22,23] In contrast, somatostatin receptor agonist and oxytocin showed an increase in fasting glucose level.[19,25]

The effects of pharmacological treatments on insulin levels were evaluated in five studies[36,39-41,43] (Table 2). All studies for insulin used only GH. Except for one study [40], insulin levels increased in four studies.[36,39,41,43] In addition, there were nine studies evaluating the effects of pharmacological treatment on fasting insulin levels[19,22,23,30,35-38,42] Studies that investigating fasting insulin levels with using GH, one study showed unchanged level,[42] and another five studies showed increased levels.[18,30,35,37,38] Non-GH treatments such as unacylated ghrelin analog, GLP-1 receptor agonist and oxytocin showed increased fasting insulin levels.[19,22,23] Of the nine studies,[19,22,23,30,35-38,42] only four studies which fasting insulin levels were expressed in mean±SD were analyzed.[18,22,30,38] Patients who received pharmacological treatment showed a nonsignificant increase in fasting insulin levels compared with the control group (MD=2.87, 95% CI: −0.88 to 6.62, p=0.13) (Fig. 2f). The analyzed results may actually be heterogeneous (I^2=71%). In the case of omitting Carrel et al. (1999), I^2 decreased from 71% to 52%. Carrel et al. (1999) is the main cause of heterogeneity.

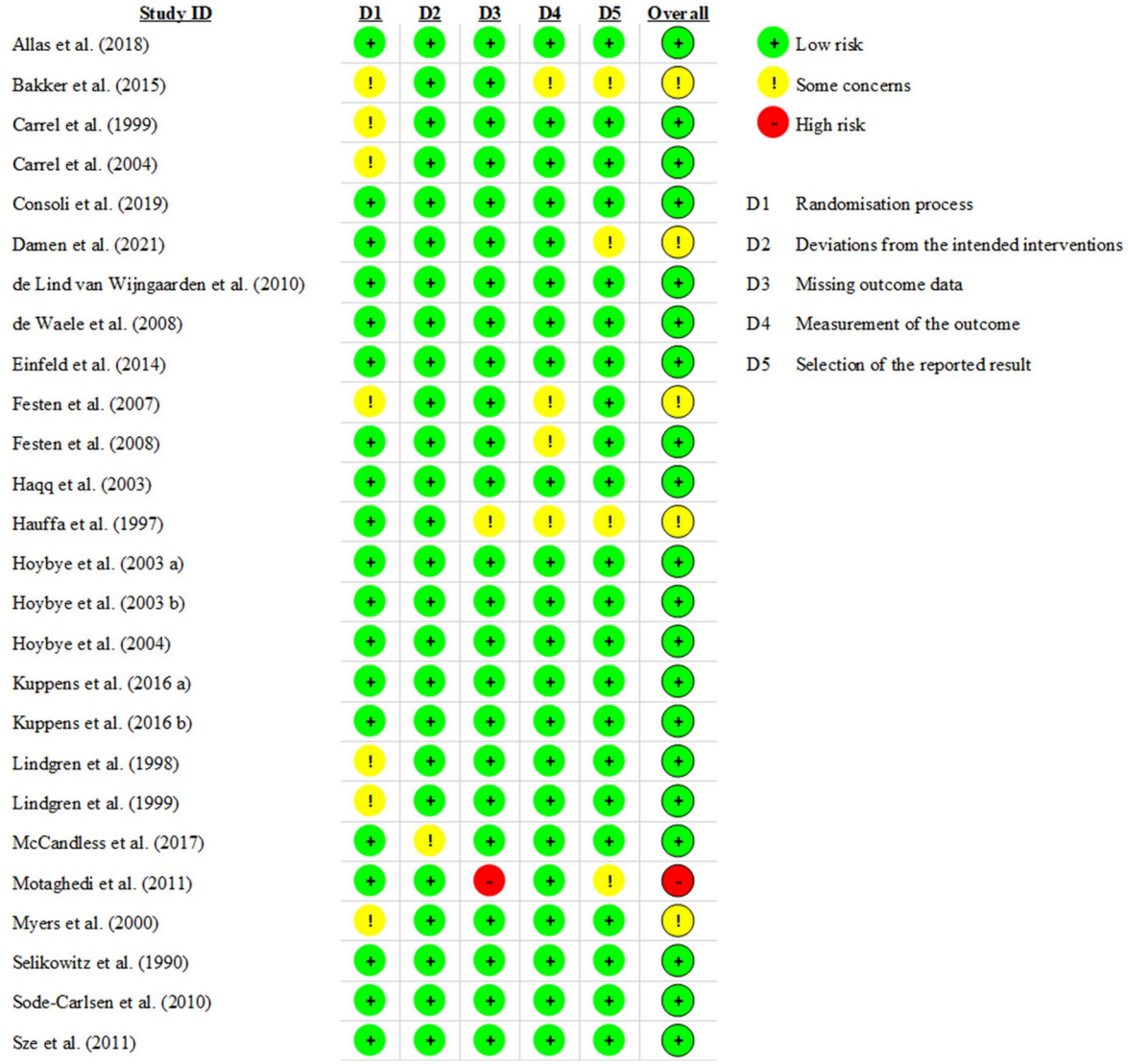

Fig. 3. Risk of bias summary

There were four studies evaluating the effects of pharmacological treatment on adiponectin levels.[21,29,35,41] All studies that investigating adiponectin levels and fasting adiponectin levels with GH were showed an increase[29,35,41] (Table 2). In the case of using selective methionine aminopeptidase 2 inhibitor,[21] adiponectin levels were also increased.

Status of hyperphagic behavior

The effects of drug treatment on the status of hyperphagic behavior were summarized in Table 2.[20,22,27] The status of hyperphagic behavior was measured using the Dykens Hyperphagia Questionnaire. The hyperphagic status was reduced in studies that using topiramate and unacylated ghrelin analog.[20,22] In contrast, there was no change in study that using oxytocin.[27]

Risk of Bias and Level of Evidence

A summary of the risk of bias evaluation is indicated in Fig. 3. In case of overall bias, five studies showed some concerns[19,30,34,35,41] and one study showed high risk,[24] but most studies showed low risk.[18,20-23,25-29,31-33,36-40,42,43] Related to the bias arising from the randomization process, most studies showed low risk,[19-29,31-34,39,40,42,43] but seven studies showed some concerns.[18,30,35-38,41] In case of bias due to deviations from intended interventions, all studies except

Table 3. GRADE evidence profile

Outcome	No. of studies (No. of participants)	Certainty assessement					Summary of findings	
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Absolute (95% CI)	Certainty
BMI	6 RCTs (238 participants)	Not serious	Not serious	Serious	Not serious	None	MD 0.73 lower (1.95 lower to 0.50 higher)	⨁⨁⨁◯ Moderate
LBM	6 RCTs (204 participants)	Not serious	Not serious	Not serious	Not serious	None	MD 1.86 higher (1.43 higher to 2.30 higher)	⨁⨁⨁⨁ High
Body fat	7 RCTs (223 participants)	Not serious	Very serious	Not serious	Not serious	None	MD 6.32 lower (10.58 lower to 2.06 lower)	⨁⨁◯◯ Low
Weight	3 RCTs (93 participants)	Not serious	Not serious	Serious	Not serious	None	MD 0.31 higher (0.73 lower to 1.36 higher)	⨁⨁⨁◯ Moderate
IGF-1	3 RCTs (100 participants)	Not serious	Not serious	Not serious	Not serious	None	MD 241.62 higher (68.59 higher to 414.64 higher)	⨁⨁⨁⨁ High
Fasting insulin	4 RCTs (184 participants)	Not serious	Serious	Serious	Not serious	None	MD 2.87 higher (0.88 lower to 6.62 higher)	⨁⨁◯◯ Low

BMI: body mass index, CI: confidence interval, IGF-1: Insulin-like growth factor 1, LBM: lean body mass, MD: mean difference, RCT: randomized controlled trial

for one showed low risk.[18-20,22-43] One study showed some concerns.[21] Related to the bias due to missing outcome data, most of the studies showed low risk,[18-23,25-33,35-43] but one study showed some concerns,[34] and another study showed high risk.[24] In case of bias in measurement of the outcome, most studies showed low risk,[18-32,36-40,42,43] but four studies showed some concerns.[33-35,41] Related to the bias in selection of the reported result, most studies showed low risk,[18,20-23,25-33,36-43] but four studies showed some concerns.[19,24,34,35]

Table 3 shows the level of evidence using the GRADEpro for the efficacy of pharmacological treatments in PWS patients compared to the control group.

Discussion

We conducted systematic review and meta-analysis that evaluated the efficacy of pharmacological treatments for PWS patient care.

According to the current study, pharmacological treatment showed effects in increasing LBM and decreasing body fat. An increment in LBM was consistently shown in a previous meta-analysis treated with GH therapy.[12,14] Increase of LBM is closely related to improving physical activity in PWS patients.[44] Because increasing physical activity is related to increasing social activity and economic advantage.[45] In addition to the improvement of LBM, higher body fat was also decreased with pharmacological treatment based on our study outcomes. Excessive body fat can cause various complications such as respiratory disorders, obstructive apnea, cardiovascular, and metabolic complications.[46] The deaths caused by these complications are more than half of the total causes of death in PWS patients.[47] Reducing body fat, it contributes to reducing complications and lowering mortality.[47] In this study, drug with GH seemed to act on more significant reduction in body fat compared to other pharmacological therapies such as oxytocin. GH metabolizes fat through fat oxidation, increasing fat utilization and reducing fat.[48] Since one of the relevant measures of body fat is BMI, this study analyzed both body fat and BMI.[49,50] The increment in BMI is closely related to obesity.[51,52] which accounts for 7% of the causes of death in patients with PWS.[47] Previous meta-analysis or systematic review results for BMI were various,[12-15] our study showed a nonsignificant decrease in BMI. These results may be caused by nonsignificant increments in weight and obvious increments in height. This may predict why BMI has not changed.

According to the types of hormone and glucose level measures, pharmacological treatment was differently associated with level change. The current study showed increased IGF-1 and fasting insulin levels after pharmacological treatment. As well, IGF-1 showed a significant increase in the previous meta-analysis,[15] IGF-1 was significantly increased in our study. Low IGF-1 levels are associated with insufficient GH secretion,[53] which results in linear growth impairment, abnormal body composition and hypothalamic dysfunction in PWS patients.[54] High IGF-1 can improve the physical ability of PWS patients by maintaining improved body composition.[44,55] Similar to low IGF-1 levels, patients with PWS show low insulin levels.[56] As previous meta-analysis studies showed a significant increase in fasting insulin,[15] in our study, both insulin levels and fasting insulin levels generally tended to increase in PWS patients through pharmacological treatment. PWS is a genetic syndrome characterized by relative hypoinsulinemia and normal or increased insulin sensitivity despite severe obesity.[57] Some PWS patients have diabetes, which may be associated with pathological obesity and subsequent insulin resistance.[58] Pharmacological treatment can prevent insulin resistance relatively, which is beneficial to the majority of GH-deficient PWS children.[58] In addition, low insulin resistance can help the lower prevalence of non-alcoholic fatty liver disease (NAFLD) or coronary disease in PWS patients.[59] The increase in insulin levels is generally associated with a decrease in glucose levels and our study also shows a tendency for glucose levels to decrease.[60] Previous meta-analysis studies showed a nonsignificant increase in fasting glucose,[14,15] whereas in this study, we could not ensure whether there was a particular tendency because the number of studies in which fasting glucose levels increased or decreased was similar. High glucose level is associated with signs of diabetes and the PWS group is at high risk for diabetes.[5] Improved diabetes status improves one of the common causes of death in patients with PWS.[47] In addition, it is possible to prevent deterioration of the quality of life due to complications.[61,62] Nevertheless, the increase in fasting glucose showed a unique characteristic accompanied by increased fasting insulin. When GH or oxytocin was used to treat PWS patients, fasting glucose and fasting insulin increased simultaneously. This is because GH and oxytocin are drugs that increase metabolism.[63,64] Glucose metabolism changes may occur due to the reverse regulatory effect of GH on insulin action through GH treatment.[65] Since the increase in fasting insulin is a risk factor for subsequent atherosclerosis in epidemiological studies, insulin can also affect the development of atherosclerosis.[66] In addition, fasting glucose reflects both basic insulin secretion and hepatic glucose production.[66] Another hormone called adiponectin is an anti-inflammatory fat cytokine, which has an inverse relationship with insulin resistance, and is a fat-derived hormone that plays an important role in protecting against diabetes and atherosclerosis.[67,68] The level of adiponectin increased in all studies. Increased adiponectin level through pharmacological treatment is consistent with the results of fat loss and can also contribute to increased insulin sensitivity.[65] In addition, it can lead to protective effects related to type 2 diabetes and cardiovascular disease.[68] Thus, pharmacological treatment was differently associated with level change, according to the types of hormone and glucose level measures.

Our study has some limitations. First, the current study did not investigate bone mineral density (BMD), one of the body-related indicators. The number of studies that investigated BMD was insufficient, so it is necessary to analyze it in other studies. Second, this study did not investigate other behavior-related problems except for hyperphagia behavior. Behavioral problems, such as compulsive behavior, were impossible for us to analyze because each study was measured using a different evaluation tool. Third, this study limited the control group to nonactive drug treatments, so we could not investigate the difference in efficacy between different medications. In the future, other studies need to analyze the differences in the effects of different drug treatments. Fourth, as recommended by the Cochrane Handbook for Systemic Reviews of Intervention, when less than 10 studies are included in meta-analysis, the power of the tests is low. There are less than 10 studies included in each meta-analysis, so we did not evaluate the publishing bias. Fifth, our study has a limitation in that various pharmacological treatments have been grouped into one intervention group. Although there were various treatment methods, these were collected according to the selection criteria that all of them were used as an intervention group to treat PWS. Sixth, this study included only GH drugs in meta-analysis of LBM and IGF-1. We found that their studies using only GH. Thus, we tried to include other treatments in meta-analysis. However, according to our inclusion criteria, studies included in LBM and IGF-1 meta-analysis did not exist any treatments except for GH. Finally, our study did not investigate safety indicators such as side effects. The purpose of this

study was to investigate the efficacy of pharmacological treatments in PWS patient care, so we did not investigate safety-related outcomes. Therefore, research to analyze safety needs to be conducted.

Conclusion

In this study, the pharmacological treatment showed an efficacy in increased LBM, decreased body fat, and increased levels of IGF-1. Additional studies are necessary to accurately search for significant treatments for PWS patients by analyzing differences in effects between drugs.

Conflicts of Interest

The authors have no conflicts of interest to declare with regards to the contents of this study.

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