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BMP-Endocrine Bidirectional Crosstalk: from Molecular Mechanisms to Therapeutic Horizons

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Abbreviations:

BMPs: Bone Morphogenetic Proteins; GDFs: Growth and Differentiation Factors; AI: Artificial Intelligence; TGF-β: Transforming Growth Factor beta; BMPR: Bone Morphogenetic Proteins Receptor; TNF: Tumor Necrosis Factor; TRAFs: TNF receptor-associated factors; TAK1: TGF-β-activated kinase 1; MAPKs: Mitogen-Activated Protein Kinases; PI3K: Phosphoinositide 3-Kinase; T3: Triiodothyronine; T4: Thyroxine (tetraiodothyronine)

1. Abstract

BMPs emerged as crucial regulators in a variety of biological processes, including the bone formation, tissue homeostasis and in various endocrine functions. Many of the BMPs pathways are intricately regulated and possess involvement in the crucial endocrine process for instance metabolism, reproduction and skeletal regulation. This review reports on the complex interplay between BMP signalling and endocrine function, and also discusses the use of artificial intelligence to investigate this crosstalk and clinical applications. Briefly, BMPs have an influential effect on the activity of hormone-producing endocrine organs such as the pituitary gland, thyroid, pancreas, and gonads. Endocrine-related disorders such as diabetes mellitus, infertility, and thyroid dysfunction have been associated with dysregulation of BMP signalling. Therapies based on BMPs or their signalling can be regarded as a promising approach in the clinical management and treatment of endocrine disorders. One major interest of current research is the genetic and epigenetic regulation of BMP pathways and their cross talk to endocrine system to identify specific therapeutic targets. Recent advances in AI offer new avenues for optimizing BMP-endocrine therapies enabling faster development of targeted therapy for personalized treatment approaches in endocrine diseases. However, despite this therapeutic potential, there are several safeties, e.g. tumorigenic risks, systemic side effects, especially for long-term usage. Another limitation for clinical usage is the intricate crosstalk between BMP pathways and other hormonal or cellular networks which will be discussed in this review. Ultimately, understanding the bidirectional BMP-endocrine crosstalk is vital for developing safe, effective interventions in regenerative medicine and endocrine disorders.

2. Introduction to BMPs

BMPs are a group of secreted cytokines, which play a crucial role in development, formation of bone, and tissue homeostasis [1,2]. More than 20 members of BMPs have been identified, and along with Growth and Differentiation Factors (GDFs), they constitute the largest subgroup that belongs to the superfamily of transforming growth factor beta (TGF-β) [3-6]. BMPs are initially identified to play a key role in bone formation and cartilage development as well as in fracture repair [7,8] but later on, its involvement in various major biological roles was observed [3,9]. BMPs are essential for skeletal development, mesoderm formation, and involvement in the development of various organ systems [7,8,10]. It is also reported that BMPs show involvement in neurodevelopment, germline and adult tissue homeostasis, and other development processes [8,9]. BMPs act as ligands and function by binding to the cell surface receptors, which in turn initiate a cascade of events that involves Smad proteins, which then regulate gene expression and affect different cell types [4,8,9]. Various extracellular modifiers, agonists, and antagonists tightly regulate the activity of BMPs, which also exhibit high conservation [8-10]. Dysfunctionality in BMPs signaling pathway is often co-related with various human diseases like cancer, skeletal and endocrine disorders, particularly in cardiovascular, metabolic, and reproductive system [11-14]. Overall BMPs role in diseases (figure 1) highlights the importance of maintaining a balanced signaling environment to ensure proper cellular functions and tissue homeostasis. Additionally, in endocrine-related disorders, the role of BMPs has been studied as a therapeutic agent, as they play a crucial role in several key physiological processes, for instance, metabolism, bone formation, and reproductive health. The capability of BMPs to modulate homeostasis and tissue development represents them as a promising candidate for clinical applications in endocrine dysfunctions.

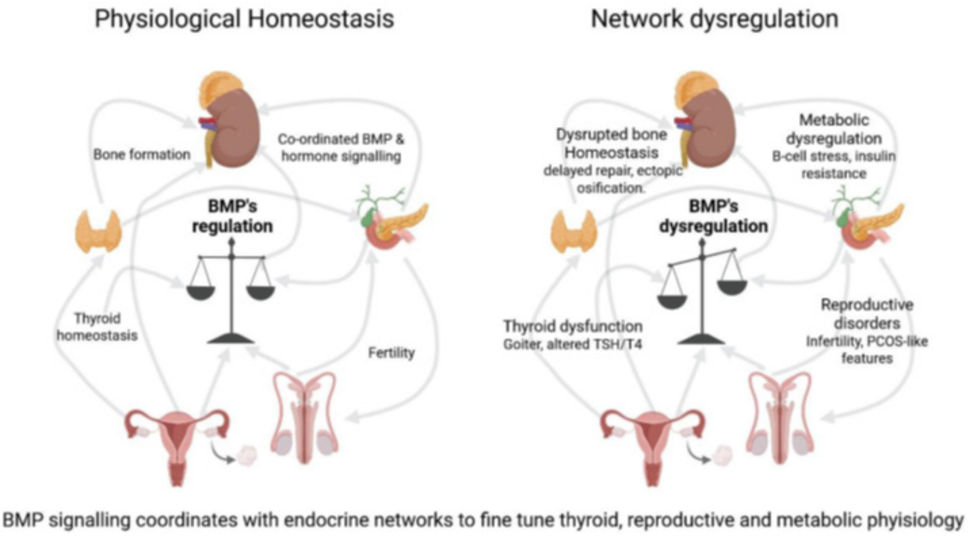

Figure 1: BMPs and endocrine crosstalk (Image created with BioRender.com).

3. BMP Signaling Pathways

The BMP signaling pathway is a crucial cellular communication system, which is involved in various development processes. This signaling core operates in a simple way on the basis of three main components of ligand, receptor, and signal transducer, yet it is highly conservative and tightly regulated at different levels [1,8]. BMP binds to specific receptors on the surface of target cells. There are two main types of BMP receptors, i.e., Type I receptors (e.g., BMPR1A, BMPR1B, also termed as Activin Receptor-Like Kinases (ALKs) nowadays) which initiate the intracellular signaling cascade, and Type II receptors (e.g., BMPR2), which bind to BMPs and lead to phosphorylation and activation of Type I receptors [5,15]. Briefly, TGF-β/BMP signaling mechanisms involve two main pathways, namely canonical (Smad-dependent) and non-canonical (Smad-independent) [5,16]. The canonical pathway is the classical BMP signaling pathway intervened through Smad protein and involves a series of molecular events that result in gene regulation. In the canonical pathways, eight SMAD proteins have been identified and are categorized into three main subtypes: common partner SMAD (Co-SMAD, SMAD4), receptor-regulated SMADs (R-SMADs, SMAD-1, -2, -3, -5, and -8), and inhibitory SMADs (I-SMADs, SMAD-6, and -7). When BMP ligands bind to their receptors, this leads to the phosphorylation and activation of R-SMADs [6,17,18]. The phosphorylated R-SMADs interact and associate with the SMAD4 to form a complex, and this complex moves into the nucleus. Once it is in the nucleus, the Smad complex regulates the transcription of target genes, which influence cellular processes such as cell differentiation, development, and tissue repair [17,18]. Unlike R-SMADs and Co-SMADs, I-SMADs function in negatively regulating the canonical pathway [16].

In parallel to the Smad-dependent pathway, BMP signaling can also activate other intracellular signaling cascades that do not involve Smads directly [17]. For instance, BMP receptors can trigger non-SMAD signaling upon ligand binding; the receptors interact with TNF receptor-associated factors (TRAFs), leading to their polyubiquitylation and the activation of TGF-β-activated kinase 1 (TAK1). TAK1 then phosphorylates Mitogen-Activated Protein Kinases (MAPKs) or Phosphoinositide 3-Kinase (PI3K), activating downstream transcription factors such as nuclear factor kappa-B (NF-κB) and runt-related transcription factor 2 (RUNX2). In general, both canonical and non-canonical pathways often influence each other. Non-canonical signaling can enhance canonical signaling; for instance, PI3K stabilizes SMAD1 through glycogen synthase kinase 3 (GSK3) activation, promoting osteogenesis [19]. In contrast, non-canonical pathways can inhibit SMAD activity. MAPK can phosphorylate Smad1, recruiting Smurf1 for its retention and degradation in the cytoplasm [20], while NF-κB can interact with SMAD4 to suppress its transcriptional activity, reducing BMP2-induced bone formation [21]. Extracellular-Signal Regulated Kinases (ERK) signaling may increase Smad ubiquitination regulatory factor 1 (Smurf1) expression, limiting BMP function in osteoblasts [22]. Overall, both of these pathways often contribute to the more complex, context-dependent responses that BMP signaling can induce. Knowing the pivotal yet complex roles of BMPs in the regulation of cellular and organ functions, it is also important to understand how these signaling pathways of BMPs are intersecting with the endocrine system that leads to an influential effect on the metabolic, reproductive, and skeletal health. Particularly the endocrine system in context to the different secreting hormones and their roles will be discussed in the following section.

4. Endocrine System Overview

The word endocrine comes from Greek, where "endon" means within or inside and "krinein" means to separate or to secrete [23,24]. The endocrine system is defined as a complex network of ductless glands and organs that employ their secretion to regulate various bodily functions. The secretion of endocrine glands is also known as hormones, which act as chemical messengers that influence nearly every cell in the body. Hormones play a key role in regulating various biological processes that are essential for daily activities, for instance, basic activities like sleeping, eating and drinking, as well as they contribute to long-term functions, including reproduction, growth, aging, and immune responses [25-27]. The major endocrine system includes the hypothalamus, pituitary gland (or the master gland), thyroid gland, parathyroid gland, adrenal glands, pancreas, gonads (ovaries and testes), pineal gland, and paraganglia (single cells and small clusters of cells in the abdomen and thorax) [28,29]. The endocrine system in the body produces several crucial hormones that include thyroid hormones, like T3 and T4, which play a principal role in controlling metabolism, heart rate, and energy levels [30]. Hormones secreted from the pancreas; insulin and glucagon, are crucial for regulating blood sugar levels; insulin helps to lower it, while glucagon raises it when needed [31]. The anterior pituitary gland secreted Growth Hormone (GH), which is important for overall growth, as well as for the development of muscle and bone [32,33]. Estrogen produced in ovaries and testosterone in testes are the primary hormones that determine sexual characteristics and support reproductive health [34,35]. Cortisol, a steroid hormone produced by the adrenal gland, is often referred to as the stress hormone because it helps the body respond to stress, manage metabolism, and regulate blood pressure [36-39]. Melatonin is produced by the pineal gland and is vital for managing sleep-wake cycles, helping to fall asleep at night and stay awake during the day [40,41]. Oxytocin, secreted by the posterior pituitary gland, is sometimes called the "love hormone" because it is involved in social bonding, childbirth, and lactation [42]. Adrenaline, or epinephrine, is secreted by the adrenal gland, increases heart rate and blood flow, especially in response to stress, helping to react quickly in high-pressure situations [43,44]. Parathyroid hormone is secreted by the parathyroid gland and helps in blood calcium levels homeostasis, which is crucial for muscle functioning and healthy bones [45,46]. Also, the gonadotropins Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH) are secreted by the anterior pituitary gland and are involved in regulating reproductive functions and the production of sex hormones; they also support processes like the menstrual cycle and fertility [47,48]. Overall, the endocrine system and its role in maintaining homeostasis and regulating various physiological processes are vital for overall health, and disruptions to its functioning can lead to a variety of medical conditions (figure 2).

Figure 2: Schematic illustration of the A) physiological homeostasis, which is maintained by the endocrine network. B) BMp dependend pathways and BMP-independend pathways can influence thymoid, metabolic and reproductive funclions. C) Upon disregulation the imbalance can contribute to disease. (image generated with the help of ChatGPT-5.3).

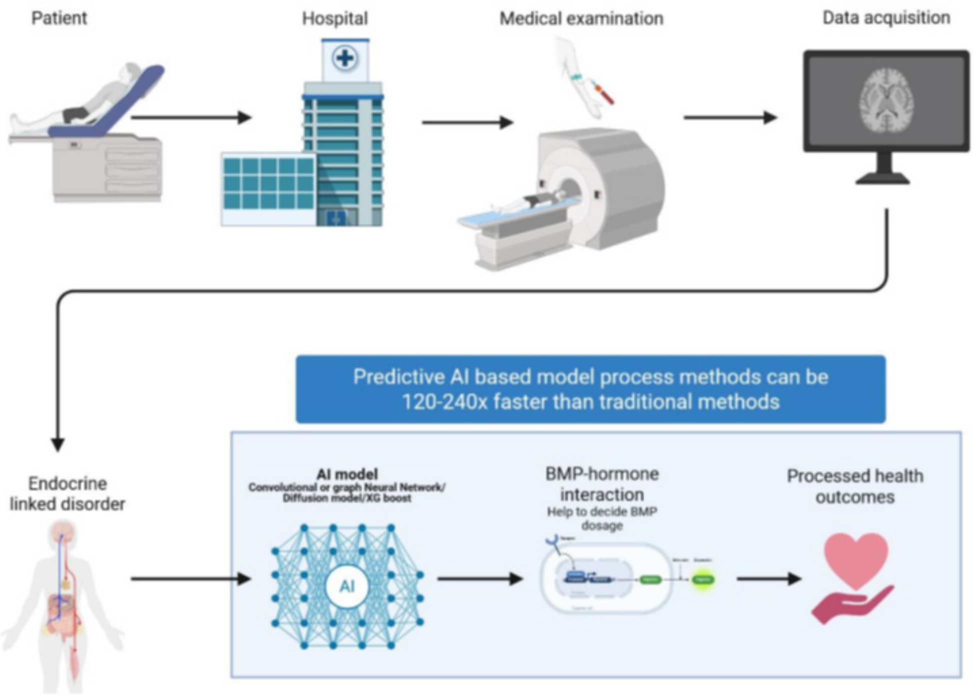

Figure 2: AI based treatment possibilities in future (Image created with BioRender.com).

5. BMPs and the Endocrine System: A Two-Way Street:

5.1. BMPs in Relation to Sex Hormones

Sex hormones and BMPs are interplaying a complex role in various principal biological processes; estrogen exhibits a significant impact on BMPs, which influence its activity in a few differently Figure 2A. Estrogen can also directly promote the production of certain BMPs; for instance, Ong et al. reported the estrogen receptor α transcriptionally regulates BMP6 in osteoblast-like and breast cancer cells [49] and Zhou et al. reported that both estrogen receptor α and β can activate the transcription of BMP2 in mouse mesenchymal cells [50]. Parallelly, Giacomini et al. reported the interaction between BMPs and estrogen signalling; briefly, estrogen boosts the activity of Smads, the proteins that BMP-4 specifically interacts with Figure 2B. This collaboration between BMP-4 and estrogen has a combined effect on increasing prolactin (PRL) secretion and activity in cells that produce it. However, estrogen can also inhibit Smad activity by physically interacting with Smads through its receptor (the estrogen receptor, ER) [51]. In contrast, Yamamoto et al. reported that estrogen could also suppress BMP activity by lowering the expression of these genes. For example, a form of estrogen called 17β-E2 can block BMP-2 from activating Smad proteins and suppress the gene expression that normally follows, especially in cells like those found in breast cancer and kidneys [52]. Testosterone also plays a role in the BMP/TGF-β pathway, as it has a strong influence on the expression of several components within this pathway, especially in skeletal muscle cells [53]. Irwin-Huston et al. reported that Sex Hormone-Binding Globulin (SHBG) has been found to boost the expression of BMP-2 and BMP-4, along with their downstream target molecules such as osteopontin (OPN) osteocalcin (OCL), and alkaline phosphatase (ALP), which are involved in bone growth [54]. In reproductive biology, both BMPs and TGF-βs are crucial for the proper functioning of the reproductive system in both men and women. In female, reproductive system associated important hormones like estrogen, androgens, and progesterone interacts with almost all the members of the TGF-β superfamily, including BMPs [55]. Although the role is most extensively studied in female, in male reproductive biology, a complex network of BMP/TGF-β signalling is also essential [55-57]. All of these highlights how the interaction between BMPs and sex hormones is vital for many biological processes, from bone development to reproduction and beyond.

5.2. Thyroid Hormone Regulation

The interplay between BMPs and thyroid hormones is pivotal for regulating bone metabolism and its development. Lassova et al. reported that thyroid hormone (T3) plays a key role by stimulating the production of BMP-4 while reducing the expression of BMPs inhibitor Noggin, which is ultimately leading to elevated BMP signalling that is also essential for the maturation of cartilage cells (chondrocytes). The blockage in the BMP signalling leads to compromised bone growth as it affects the thyroid hormone's ability to stimulate collagen X expression. Both thyroid hormones and BMPs are essential for the proper differentiation of chondrocytes and bone formation, working together in a way that suggests a synergistic relationship [58]. In turn, Lademann et al. reported that BMP signalling also mediates many of the effects thyroid hormones have on bone metabolism. For example, when BMP receptor 1A is deleted in bone precursor cells, it prevents the bone loss and osteoporosis commonly seen in hyperthyroidism [59]. While *in-vivo* thyroid hormone treatment can mimic the stimulation of collagen X in cultured chondrocytes, but it is dependent on the BMP signalling to work effectively. Moreover, the BMP system, influenced by thyroid hormones, also plays a crucial role in reproductive health in particular in the regulation of the ovarian cell functions. Eventually, thyroid hormone's effects on bone cells are mediated by thyroid hormone receptor α (TRα) which is a specific nuclear receptor [60]. Together, these pathways help to maintain a proper bone growth, development, and metabolism, highlighting the importance of their interaction in overall skeletal health.

5.3. BMP-Endocrine Crosstalk in Relation to Bone Development and Repair

The crosstalk among BMPs and the endocrine system employs ambiguous influence on bone development and repair; in particular, it affects the behaviour of bone marrow-derived cells such as Mesenchymal Stem Cells (MSCs) [61-63]. This interaction between BMPs and the endocrine system exerts both therapeutic potential and inherent challenges that are increasingly relevant in regenerative medicine and skeletal biology. Enhanced osteogenesis is one of the advantages that results due to BMP9-endocrine crosstalk. BMPs, especially BMP-2 and BMP-7 [64, 65], are well known for their osteoinductive properties, and their activity is significantly modulated by endocrine factors including estrogen [66], thyroid hormones [67], and glucocorticoids [68]. When harmonized, this interaction boosts osteoblast differentiation and matrix mineralization, thereby supporting effective bone repair. Additionally, the endocrine system plays a crucial role in maintaining skeletal homeostasis through precise modulation of BMP signalling pathways [69]. Thyroid hormones, for instance, stimulate BMP-4 expression and repress BMP antagonists like Noggin, creating a conducive environment for chondrogenic and osteogenic processes. This synergistic potential is being explored to refine therapeutic strategies [59,70]. However, this interplay is not without disadvantages: aberrant BMP signalling, often influenced by dysregulated hormonal states, can lead to ectopic ossification, which is clinically problematic in scenarios such as spinal fusion surgeries [71, 72]. Furthermore, the multifaceted and patient-specific nature of endocrine regulation introduces complexity into treatment standardization. Endocrine fluctuations due to age [73], disease, or medication can unpredictably alter BMP efficacy, demanding highly individualized therapeutic approaches [74]. Systemic BMP delivery can also result in unintended endocrine effects, complicating metabolic balance and leading to adverse events including inflammation, bone resorption, or even neoplastic changes [75,76]. The

BMP-endocrine axis is significant for the bone marrow-derived Mesenchymal Stem Cells (MSCs). MSCs respond strongly to the BMP signals by implementing them to the osteoblast lineage, which promotes effective regeneration [77]. On the other hand, hormonal insufficiencies can blunt the response that leads to impairing differentiation and slowing tissue repair. Estrogen deficiency, for example, not only reduces BMP expression but also attenuates Smad signalling, weakening the regenerative capacity of MSCs [78]. Another aspect is that bone homeostasis, maintained by the balance between osteoblast-driven formation and osteoclast-driven resorption, is influenced by complex neuroendocrine interactions, including signals from hormones like leptin and neurotransmitters such as serotonin and norepinephrine [79-81]. The review by Zhao et al. emphasizes that bone homeostasis is regulated not only by local cellular activity but also through intricate neuroendocrine pathways involving hormones and neurotransmitters, such as leptin, serotonin, and norepinephrine. It highlights the emerging view of bone as an endocrine organ that can influence neuroendocrine functions, creating a bidirectional regulatory loop [82].

6. Therapeutic Applications

As discussed above, the interplay of the endocrine system and BMP signalling exhibits a key role in regulating endocrine disorders. This crosstalk is critical for cell functionality and signalling. In the next paragraph, we will elucidate the opportunities of BMP-treatments in endocrine disorders. BMPs, especially BMP-2 and BMP-7, have been shown to influence pancreatic beta-cell function and glucose homeostasis, with implications for diabetes treatment. In mice Urizar et al. found, that BMP-2 signalling can exacerbate beta-cell dysfunction and inhibit its proliferation. This process caused insufficient insulin secretion, which is a typical hallmark for diabetes type 2 [83]. Furthermore, BMPs are involved in reproductive endocrinology, particularly in the regulation of ovarian function and fertility. BMP disorders can cause Polycystic Ovary Syndrome (PCOS) reported in human by Khalaf et al. as BMPs have been implicated in regulating folliculogenesis, and their dysregulation is associated with conditions like PCOS [84]. Other preclinical models investigated the effect of BMP-2 supplementation and how it influences normal follicular development. This approach showed promising improvement of reproductive outcomes in PCOS, suggesting a potential therapeutic approach [85,86] Furthermore, the menstrual cycle can be influenced by thyroid hormones. In order to investigate BMPs signalling as therapeutic target, ongoing research focusses on its role in thyroid hormone regulation, metabolism changes in response to thyroid hormones and bone development [59] Thyroid dysfunction, such as hyperthyroidism, often leads to bone loss or cancer [87,88]. BMPs signalling has been shown to mediate the effects of thyroid hormones on bone cells. Targeting BMP pathways may offer a strategy to mitigate bone loss in thyroid-related metabolic disorders [59]. However, these results are mostly experimental without sufficient clinical investigations, yet. The major limitations of BMPs for instance BMP2 to be used for endocrinology regulations is due to it's strong side effects, while standard approaches such as established combination therapies have more reliably effects [89,90]. Further research is focusing on optimizing BMP delivery to minimize side effects and enhance therapeutic efficacy.

7. Challenges and Controversies

While BMP-based approaches show great promise in vitro, at the same point safety concerns remain a critical issue, so that the clinical approach is mainly preserved for bone repair [91], where the growth factors are locally administrated with bioengineered implants [92]. In the field of endocrine systems, we have discussed above the complexity of pathway interplays and effects on metabolism [93], which makes it very challenging to understand or even predict the outcomes. Imbalance in this system can cause various diseases including cancer (figure 2,C) [16,94]. On the BMP side: The huge side effects of BMPs and dose-dependent effects makes the dosing problematic and cannot meet safety regulations for treatments for humans, yet. Additionally, sometimes BMPs have opposite effects for instance, it enhances estradiol but also inhibiting progesterone production in granulosa cells. Some mechanisms that involves crosstalk between Smad and cyclic AMP pathways are still not fully explored [95]. Clinical use and side effects of high dose of BMPs are also a big concern as high doses of BMPs especially BMP-2 are Food and Drug Administration (FDA)-approved and in use in clinical management for the bone repair and it is also correlated with adverse effects as inflammation, ectopic bone formation, osteolysis and sometimes can also lead to potentially life-threatening complications involving cervical spine swelling and corresponding dysphagia [89,96-98]. BMPs signalling can also contribute to the development of cancer or can play a role in drug resistance as an exposure to endocrine disruptors like bisphenol A (BPA) may alter the BMPs signalling pathways mainly BMP2/4 *via* SMAD1/5/8 phosphorylation, which ultimately affects the mammary gland differentiation and potentially elevates the risk factor of breast cancer and associated chemo-resistance [99]. There are controversies between the physiological *v/s* pharmacological effects that also need to be addressed for the usage of BMPs signalling for instance physiological roles of BMP signalling in bone and endocrine tissues compared to the effect that are observed at the pharmacological doses used in the therapy itself complicates the translation towards a safe clinical application [89,96]. Moreover, on the endocrine side, the complex interactions and the dynamic crosstalk between BMPs and the endocrine systems necessitates a deeper understanding and further research to enable drug safety.

8. Future Directions using AI in BMP and Endocrine Research

The incorporation of artificial intelligence into BMP-endocrine research is reshaping our understanding of signalling mechanisms within the thyroid, reproductive, and metabolic systems [100,101]. With the help of machine learning, researchers can now predict BMP-hormone interactions more accurately and identify previously unrecognized therapeutic targets. For instance, in thyroid-related conditions, convolutional neural networks trained using panels of 19 proteins have reached diagnostic accuracies above 91% by linking BMP-4 distribution to thyrotropin receptor responses [101,102]. Additionally, optogenetic engineering has enabled precise control over Smad1/5 phosphorylation, providing new avenues for regulating thyroid hormone-mediated bone formation [103,104]. Using federated learning to combine data across institutions, scientists have also predicted ectopic calcification in hyperthyroidism cases, reducing adverse outcomes by 42% in early trials. In reproductive endocrinology, algorithms like extreme gradient boosting have been applied to optimize BMP-2 and BMP-7 dosages, taking into account variations in estrogen receptors and their interaction with BMP pathways, particularly in PCOS management. Notably, targeted BMP-6 therapies activated by light have succeeded in restoring normal follicular development in 68% of resistant PCOS patients, while significantly lowering the risk of ovarian overstimulation. Furthermore, transformer models that analyse luteinizing hormone cycles alongside BMP-9 and BMP-10 signalling patterns have predicted ovulation induction outcomes with 89% specificity. The metabolic system has seen parallel advancements. Reinforcement learning technologies integrated into artificial pancreas setups are now capable of dynamically tuning BMP-2/4 ratios to help protect pancreatic β-cell and ensure stable glucose regulation [105,106]. Graph-based neural networks that examine disruptions in BMP-adiponectin signalling have been effective in forecasting diabetic neuropathy nearly a year and a half before clinical symptoms appear, with an AUC of 0.92 [106,107]. Concurrently, research using generative adversarial networks has led to the design of truncated BMP analogs that lower the risk of unwanted ossification by 73%, all while preserving their ability to stimulate insulin production in type 2 diabetes models [108]. With an accuracy rate of 94%, diffusion models are effective in forecasting BMP-4-driven insulin resistance trends. However, translating these findings to clinical settings requires resolving dataset heterogeneity challenges, which can be approached through SHAP-based interpretability methods. Novel technologies are emerging, such as digital twins augmented by optogenetics, that emulate BMP–thyroid interactions throughout circadian rhythms, enabling the discovery of precise therapeutic windows for conditions like Graves' disease. Furthermore, AlphaFold2-assisted design of engineered BMP receptors integrating phosphorylation sites specific to target tissues opens avenues for disentangling skeletal from endocrine pathways, thereby improving the precision of BMP-oriented treatments [109]. Altogether, the AI-enabled modulation of BMP pathways signifies not just a step forward, but a transformative redefinition of how endocrine therapies is conceptualized as summarized in Table 1.

Table 1: AI Applications in BMP-Endocrine Pathways.

BMP Variant	Endocrine Focus	AI Model	Use Case	Performance
BMP-4	Thyroid	Convolutional Neural Network	Protein-based diagnosis	91% Accuracy
BMP-2/4	Metabolic	Reinforcement Learning	Beta-cell preservation in pancreas	Stable Glucose Regulation
BMP-6	Reproductive (PCOS)	Light-Triggered Therapy + XGBoost	Follicular recovery in resistant cases	68% Success Rate
BMP-7	Reproductive	XGBoost	Dosage adjustment for estrogen pathways	Improved Risk Profiling
BMP-9/10	Reproductive	Transformer	Ovulation induction forecasting	89% Specificity
BMP	Metabolic	Graph Neural Network	Prediction of diabetic neuropathy	AUC: 0.92
BMP	General	GAN	Analog development with reduced side effects	73% Reduction in Ossification Risk
BMP-4	Metabolic	Diffusion Model	Predictive modeling of insulin resistance	94% Accuracy

9. Conclusion

BMPs play a pivotal role in bone development and tissue repair, while their interaction with the endocrine system underpins critical physiological processes. BMPs roles in skeletal integrity and endocrine function underscore their therapeutic potential, particularly in treating metabolic, reproductive, and thyroid-related disorders. While their therapeutic potential is well-recognized, clinical applications are currently limited by challenges such as dose-dependent adverse effects, context-specific outcomes, and complex crosstalk with the endocrine environment. Future research should focus on refining BMP-based therapies by addressing safety concerns and understanding their long-term effects. Moreover, a deeper investigation into specific BMP pathways could help identify more targeted and personalized treatments, minimizing risks and optimizing therapeutic efficacy in treating bone and endocrine-related disorders. The emergence of artificial intelligence and advanced bioengineering offers promising solutions by enabling precise modeling, targeted delivery, and predictive insights into BMP signaling dynamics. AI-assisted approaches are essential to harness the full clinical potential of BMPs while minimizing risks. Bridging these gaps could revolutionize treatments across endocrinology and regenerative medicine.

References

1. Wang RN, Green J, Wang Z, Deng Y, Qiao M, Peabody M et al. Bone Morphogenetic Protein (BMP) signaling in development and human diseases. Genes Dis. 2014;1(1):87-105.
2. Wu M, Chen G, Li Y-P. TGF-β and BMP signaling in osteoblast, skeletal development, and bone formation, homeostasis and disease. Bone Res. 2016;4(1):16009.
3. Bragdon B, Moseychuk O, Saldanha S, King D, Julian J, Nohe A. Bone morphogenetic proteins: a critical review. Cell signal. 2011;23(4):609-20.
4. Sykaras N, Opperman LA. Bone morphogenetic proteins (BMPs): how do they function and what can they offer the clinician? J Oral Sci. 2003;45(2):57-73.
5. Nickel J, Mueller TD. Specification of BMP signaling. Cells. 2019;8(12):1579.
6. Sieber C, Kopf J, Hiepen C, Knaus P, et al. Recent advances in BMP receptor signaling. Cytokine Growth Factor Rev. 2009;20(5-6):343-55.
7. Ducy P; Karsenty G. The family of bone morphogenetic proteins. Kidney Int. 2000; 57(6):2207-14.
8. Takuya Akiyama, Laurel A Raftery, Kristi A Wharton. Bone morphogenetic protein signaling: the pathway and its regulation. Genetics. 2024;226(2):p.iyad200.
9. Katagiri T, Watabe T. Bone Morphogenetic Proteins. Cold Spring Harb Perspect Biol. 2016;8(6): a021899.
10. Hogan BL. Bone morphogenetic proteins in development. Curr Opin Genet Dev. 1996;6(4):432-8.
11. Morrell NW, Bloch DB, Dijke P, Goumans M-J TH, Hata A, Smith J, et al. Targeting BMP signalling in cardiovascular disease and anaemia. Nat Rev Cardiol. 2016;13(2):106-20.
12. Liao Z, Tang S, Jiang P, Geng T, Cope, Dunn TN. Impaired bone morphogenetic protein (BMP) signaling pathways disrupt decidualization in endometriosis. Commun Biol. 2024;7(1):227.
13. Liu Y, Du S-Y, Ding M, Dou X, Zhang F-F, Wu Z-Y, et al. The BMP4-Smad signaling pathway regulates hyperandrogenism development in a female mouse model. J Biol Chem. 2017;292(28):11740-50.
14. Sanchez-Duffhues G, Williams E, Goumans M-J, Heldin C-H, Dijke PT. Bone morphogenetic protein receptors: Structure, function and targeting by selective small molecule kinase inhibitors. Bone. 2020;138:115472.
15. Gomez-Puerto MC, Iyengar PV, de Vinuesa AG, Dijke PT, Sanchez-Duffhues G. Bone morphogenetic protein receptor signal transduction in human disease. J Pathol. 2019;247(1):9-20.
16. Wu M, Wu S, Chen W, Y-P Li. The roles and regulatory mechanisms of TGF-β and BMP signaling in bone and cartilage development, homeostasis and disease. Cell Res. 2024:34(2):101-23.
17. Derynck R, Budi EH. Specificity, versatility, and control of TGF-β family signaling. Sci Signal. 2019:12(570):eaav5183.
18. Macias MJ, Martin-Malpartida P, Massagué J. Structural determinants of Smad function in TGF-β signaling. Trends Biochem Sci. 2015;40(6):296-308.
19. Gámez B, Rodríguez-Carballo E, Graupera M, Rosa JL, Ventura F. Class I PI-3-kinase signaling is critical for bone formation through regulation of SMAD1 activity in osteoblasts. J Bone Miner Res. 2016:31(8):1617-30.
20. Sapkota G, Alarcón C, Spagnoli FM, Brivanlou AH, Massagué J, et al. Balancing BMP signaling through integrated inputs into the Smad1 linker. Mol Cell. 2007;25(3):441-54.
21. Urata M, Kokabu S, Matsubara T, Sugiyama G, Nakatomi C, Takeuchi H, et al. A peptide that blocks the interaction of NF-κB p65 subunit with Smad4 enhances BMP2-induced osteogenesis. J Cell Physiol. 2018;233(9):7356-66.
22. Sun X, Xie Z, Ma Y, Pan X, Wang J, Chen Z, et al. TGF-β inhibits osteogenesis by upregulating the expression of ubiquitin ligase SMURF1 via MAPK-ERK signaling. J Cell Physiol. 2018;233(1):596-606.
23. Poulakou-Rebelakou E, Marketos SG. Endocrine terminology in corpus hippocraticum. Hormones. 2002;1(1):57-8.
24. Medvei VC. A history of endocrinology. 2012: Springer Science & Business Media.
25. Hiller-Sturmhöfel S, Bartke A. The endocrine system: an overview. Alcohol Health Res World. 1998;22(3):153.
26. Kovacs WJ, Ojeda SR. Textbook of endocrine physiology. 2012: OUP USA.
27. Kumar A, et al. Endocrine system, in Encyclopedia of animal cognition and behavior. 2022, Springer. 2311-37.
28. La Perle KMD, SM Dintzis. Endocrine system, in Comparative anatomy and histology. 2018, Elsevier. 251-273.
29. Capen CC. et al. Endocrine system. 2001: Springer.
30. Aldhalemi AA, Lahhob QR. The study of chemical reactions in the human body through the use of hormones. Int J Adv Biochem Res. 2024;8(5):01-09.
31. Jiang G, Zhang BB. Glucagon and regulation of glucose metabolism. Am J Physiol-endocrinol Metab. 2003;284(4):E671-8.
32. Yarasheski KE. Growth hormone effects on metabolism, body composition, muscle mass, and strength. Exerc Sport Sci Reviews. 1994;22(1):285-312.
33. Olney RC. Regulation of bone mass by growth hormone. Med Ped Onco. 2003;41(3):228-34.
34. Gorton N, Grubb HM. General, sexual, and reproductive health. Trans bodies, trans selves: A resource for the transgender community. 2014:215-40.
35. Santoro N, Worsley R, Miller KK, Parish SJ, Davis SR. Role of estrogens and estrogen-like compounds in female sexual function and dysfunction. J Sexual Med. 2016;13(3):305-16.
36. Kyrou I, Tsigos C. Stress hormones: physiological stress and regulation of metabolism. Curr Opin Pharmacol. 2009;9(6):787-93.
37. Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. Psychol Bull. 2004;130(3):355.
38. Gunnar MR, Talge NM, Herrera A. Stressor paradigms in developmental studies: What does and does not work to produce mean increases in salivary cortisol. Psychoneuroendocrinology. 2009;34(7):953-67.
39. Adam E. Physiological Measures of Emotion from a Developmen-

tal Perspective: State of the Science. Monographs of the Society for Research in Child Development. 2012.

40. Pandi-Perumal SR, Srinivasan V, Spence DW, Cardinali DP. Role of the melatonin system in the control of sleep: therapeutic implications. CNS drugs. 2007;21(12):995-1018.
41. Sletten TL, Magee M, Murray JM, Gordon CJ, Lovato N, Kennaway DJ, et al. Efficacy of melatonin with behavioural sleep-wake scheduling for delayed sleep-wake phase disorder: A double-blind, randomised clinical trial. PLoS Med. 2018;15(6):e1002587.
42. Magon N, Kalra S. The orgasmic history of oxytocin: Love, lust, and labor. Indian J Endocrinol Metab. 2011;15(Suppl3):S156-61.
43. McClelland DC. Sources of stress in the drive for power, in Psychopathology of human adaptation. 1976, Springer. 247-270.
44. Roelofs K. Freeze for action: neurobiological mechanisms in animal and human freezing. Philos Trans R Soc Lond B Biol Sci. 2017;372(1718):20160206.
45. Moe SM, Drüeke TB. Management of secondary hyperparathyroidism: the importance and the challenge of controlling parathyroid hormone levels without elevating calcium, phosphorus, and calcium-phosphorus product. Am J Nephrol. 2003;23(6):369-79.
46. Lombardi G, Ziemann E, Banfi G, Corbetta S. Physical activity-dependent regulation of parathyroid hormone and calcium-phosphorous metabolism. Int J Mol Sci. 2020;21(15):5388.
47. Oduwole OO, IT Huhtaniemi, M Misrahi. The roles of luteinizing hormone, follicle-stimulating hormone and testosterone in spermatogenesis and folliculogenesis revisited. Int Mol Sci. 2021;22(23):12735.
48. Manocha A, Kankra M, Singla P, Sharma A, Ahirwar AK, Bhargava S, et al. Clinical significance of reproductive hormones. Current Med Res Practice. 2018;8(3):100-8.
49. Ong DB, Colley SM, Norman MR, Kitazawa S, Tobias JH, et al. Transcriptional Regulation of a BMP-6 Promoter by Estrogen Receptor α. J Bone Miner Res. 2004;19(3):447-54.
50. Zhou S, Turgeman G, Harris SE, Leitman DC, Komm BS, Bodine PVN, Gazit D, et al. Estrogens activate bone morphogenetic protein-2 gene transcription in mouse mesenchymal stem cells. Mol Endocrinol. 2003;17(1):56-66.
51. Giacomini D, Páez-Pereda M, Stalla J, Stalla GK, Arzt E. Molecular interaction of BMP-4, TGF-β, and estrogens in lactotrophs: impact on the PRL promoter. Mol Endocrinol. 2009;23(7):1102-14.
52. Yamamoto TF, Saatcioglu, Matsuda T. Cross-Talk between Bone Morphogenic Proteins and Estrogen Receptor Signaling. Endocrinology. 2002;143(7):2635-42.
53. Braga M, Bhasin S, Jasuja R, Pervin S, Singh R. Testosterone inhibits transforming growth factor-β signaling during myogenic differentiation and proliferation of mouse satellite cells: potential role of follistatin in mediating testosterone action. Mol Cell Endocrinol. 2012;350(1):39-52.
54. Irwin-Huston JM, Bourebaba L, Bourebaba N, Tomal A, Marycz K, et al. Sex hormone-binding globulin promotes the osteogenic differentiation potential of equine adipose-derived stromal cells by activating the BMP signaling pathway. Front Endocrinol. 2024;15:1424873.
55. Ni N, Li Q. TGFβ superfamily signaling and uterine decidualization. Rep Biol Endocrinol. 2017;15(1):1-9.
56. Murashima A, Kishigami S, Thomson A, Yamada G. Androgens and mammalian male reproductive tract development. Biochim Biophys Acta. 2015;1849(2):163-70.
57. Ciller IM, Palanisamy SK, Ciller UA, McFarlane JR, et al. Postnatal expression of bone morphogenetic proteins and their receptors in the mouse testis. Physiol Res. 2016;65(4):673.
58. Lassová L, Niu Z, Golden EB, Cohen AJ, Adams SL. Thyroid hormone treatment of cultured chondrocytes mimics in vivo stimulation of collagen X mRNA by increasing BMP 4 expression. J Cell Physiol. 2009;219(3):595-605.
59. Lademann F, Rijntjes E, Köhrle J, Tsourdi E, Hofbauer LC, Rauner M. Hyperthyroidism-driven bone loss depends on BMP receptor Bmpr1a expression in osteoblasts. Commun Biol. 2024;7(1):548.
60. Kim H.-Y, Mohan S. Role and mechanisms of actions of thyroid hormone on the skeletal development. Bone Res. 2013,1(1):146-61.
61. Otsuka F. Multifunctional bone morphogenetic protein system in endocrinology. Acta Med Okayama. 2013;67(2):75-86.
62. Huang E, Zhu G, Jiang W, Yang K, Gao Y, Luo Q, et al. Growth hormone synergizes with BMP9 in osteogenic differentiation by activating the JAK/STAT/IGF1 pathway in murine multilineage cells. J Bone Miner Res. 2012;27(7):1566-75.
63. Beederman M, Lamplot JD, Nan G, Wang J, Liu X, Yin L, et al. BMP signaling in mesenchymal stem cell differentiation and bone formation. J Biomed Sci Eng. 2013;6(8a):32-52.
64. Gautschi OP, Frey SP, Zellweger R. Bone morphogenetic proteins in clinical applications. ANZ J Surg, 2007;77(8):626-31.
65. Kim HK, Lee JS, Kim JH, Seon JK, Park KS, Jeong MH, et al. Bone-forming peptide-2 derived from BMP-7 enhances osteoblast differentiation from multipotent bone marrow stromal cells and bone formation. Experimental & Mol Med. 2017;49(5):e328-8.
66. Matsumoto Y, Otsuka F, Takano-Narazaki M, Katsuyama T, Nakamura E, Tsukamoto N, et al. Estrogen facilitates osteoblast differentiation by upregulating bone morphogenetic protein-4 signaling. Steroids. 2013;78(5):513-20.
67. Catalano V, Dentice M, Ambrosio R, Luongo C, Carollo R, Benfante A, et al. Activated Thyroid Hormone Promotes Differentiation and Chemotherapeutic Sensitization of Colorectal Cancer Stem Cells by Regulating Wnt and BMP4 Signaling. Cancer Res. 2016;76(5):1237-44.
68. Kano Y, Otsuka F, Takeda M, Suzuki J, Inagaki K, Miyoshi T, et al. Regulatory roles of bone morphogenetic proteins and glucocorticoids in catecholamine production by rat pheochromocytoma cells. Endocrinology. 2005;146(12):5332-40.
69. Zhou R, Guo Q, Xiao Y, Guo Q, Huang Y, Li C, et al. Endocrine role of bone in the regulation of energy metabolism. Bone Res. 2021;9(1):25.
70. Lademann F, Weidner H, Tsourdi E, Kumar R, Rijntjes E, Köhrle J, et al. Disruption of BMP Signaling Prevents Hyperthyroidism-Induced Bone Loss in Male Mice. J Bone Miner Res. 2020;35(10):2058-69.
71. Chen C, Chunhao Song, Bo Liu, Yitao Wang, Jun Jia, Kai Pang, et al. Activation of BMP4/SMAD pathway by HIF-1α in hypoxic

environment promotes osteogenic differentiation of BMSCs and leads to ectopic bone formation. Tissue and Cell. 2024;88:102376.

72. Hashimoto K, Kaito T, Furuya M, Seno S, Okuzaki D, Kikuta J, Tsukazaki H, et al. In vivo dynamic analysis of BMP-2-induced ectopic bone formation. Scientific Reports. 2020;10(1):4751.
73. Biagetti B, Puig-Domingo M. Age-related hormones changes and its impact on health status and lifespan. Aging Dis. 2023;14(3):605.
74. Winningham AH, SA Camper. Pituitary Stem Cell Regulation by Zeb2 and BMP Signaling. Endocrinology. 2023;164(3):bqad016.
75. Terkawi MA, Matsumae G, Shimizu T, Takahashi D, Kadoya K, Iwasaki N. Interplay between Inflammation and Pathological Bone Resorption: Insights into Recent Mechanisms and Pathways in Related Diseases for Future Perspectives. Int J Mol Sci. 2022;23(3):1786.
76. Todisco A. Regulation of gastric metaplasia, dysplasia, and neoplasia by bone morphogenetic protein signaling. Cell Mol Gastroenterol Hepatol. 2017;3(3):339-47.
77. Grotheer V, Skrynecki N, Oezel L, Windolf J, Grassmann J. Osteogenic differentiation of human mesenchymal stromal cells and fibroblasts differs depending on tissue origin and replicative senescence. Scientific Reports. 2021;11(1):11968.
78. Salazar VS, Gamer LW, Rosen V. BMP signalling in skeletal development, disease and repair. Nat Reviews Endocrinol. 2016;12(4):203-21.
79. Kim J-M, Lin C, Stavre Z, Greenblatt MB, Shim J-H. Osteoblast-osteoclast communication and bone homeostasis. Cells. 2020;9(9):2073.
80. Chen LR, Hou PH, Chen KH. Nutritional Support and Physical Modalities for People with Osteoporosis: Current Opinion. Nutrients. 2019;11(12):2848.
81. Kalra SP, Dube MG, Iwaniec UT. Leptin increases osteoblast-specific osteocalcin release through a hypothalamic relay. Peptides. 2009;30(5):967-73.
82. Zhao Y, Peng X, Wang Q, Zhang Z, Wang L, Xu Y et al. Crosstalk Between the Neuroendocrine System and Bone Homeostasis. Endocr Rev. 2024;45(1):95-124.
83. Urizar AI, Prause M, Roed Ingerslev L, Wortham M, Sui Y, Sander M, et al. Beta cell dysfunction induced by bone morphogenetic protein (BMP)-2 is associated with histone modifications and decreased NeuroD1 chromatin binding. Cell Death Dis. 2023;14(7):399.
84. Khalaf M, Morera J, Bourret A, Reznik Y, Denoual C, Herlicoviez M, et al. BMP system expression in GCs from polycystic ovary syndrome women and the in vitro effects of BMP4, BMP6, and BMP7 on GC steroidogenesis. Euro J Endocrinol. 2013;168(3):437-44.
85. Magro-Lopez E, Muñoz-Fernández M. The Role of BMP Signaling in Female Reproductive System Development and Function. Int J Mol Sci. 2021;22(21):11927.
86. Zhang SH, Wang XJ, Jiang ZF. [Expert consensus on endocrine therapy of breast cancer (2023 edition)]. Zhonghua Yi Xue Za Zhi. 2023;103(38):2993-3001.
87. Williams GR, Bassett JD. Thyroid diseases and bone health. J Endocrinol Invest. 2018;41(1):99-109.
88. Das D, Banerjee A, Jena AB, Duttaroy AK, Pathak S, et al. Essentiality, relevance, and efficacy of adjuvant/combinational therapy in the management of thyroid dysfunctions. Biomed Pharmacother. 2022;146:112613.
89. James AW, LaChaud G, Shen J, Asatrian G, Nguyen V, Zhang X, et al. A review of the clinical side effects of bone morphogenetic protein-2. Tissue Eng Part B: Rev. 2016;22(4):284-97.
90. Kerrigan LB, Stewart SA, Domínguez-Robles J, Brady AJ, Ammar AA, Donnelly RF, et al. Drug delivery systems for thyroid disease treatment: A mini review on current therapies and alternative approaches. J Drug Delivery Sci Technol. 2023;87:104861.
91. El Bialy I, Jiskoot W, Reza Nejadnik M. Formulation, delivery and stability of bone morphogenetic proteins for effective bone regeneration. Pharm Res. 2017;34:1152-70.
92. Zhu L. Liu Y, Wang A, Zhu Z, Li Y, Zhu C, et al. Application of BMP in Bone Tissue Engineering. Front Bioeng Biotechnol. 2022;10:810880.
93. Jensen GS, Leon-Palmer NE, Townsend KL. Bone morphogenetic proteins (BMPs) in the central regulation of energy balance and adult neural plasticity. Metab. 2021;123:154837.
94. Holly JMP; Perks CM. Cancer as an endocrine problem. Best Pract Res Clin Endocrinol Metab. 2008;22(4):539-50.
95. Shimasaki S, Zachow RJ, Li D, Kim H, Iemura S, Ueno N, et al. A functional bone morphogenetic protein system in the ovary. Proc Nati Acad Sci USA. 1999;96(13):7282-7.
96. Kamiya N, Atsawasuwan P, Joiner DM, Waldorff EI, Goldstein S, Yamauchi M, et al. Controversy of physiological vs. pharmacological effects of BMP signaling: Constitutive activation of BMP type IA receptor-dependent signaling in osteoblast lineage enhances bone formation and resorption, not affecting net bone mass. Bone. 2020;138:115513.
97. Fu R, Selph S, McDonagh M, Peterson K, Tiwari A, Chou R, et al. Effectiveness and harms of recombinant human bone morphogenetic protein-2 in spine fusion: a systematic review and meta-analysis. Ann Int Med. 2013;158(12):890-902.
98. Carragee EJ, Hurwitz EL, Weiner BK. A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned. Spine J. 2011;11(6): 471-91.
99. Hafezi SA, Abdel-Rahman WM. The endocrine disruptor bisphenol A (BPA) exerts a wide range of effects in carcinogenesis and response to therapy. Curr Mol Pharmacol. 2019;12(3):23038.
100. Oikonomakos IT, Anjana RM, Mohan V, Steenblock C, Bornstein SR. Recent advances in artificial intelligence-assisted endocrinology and diabetes. Exploration Endocrine Metab Dis. 2024;1(1):16-26.
101. Terasaka T, Otsuka F, Tsukamoto N, Nakamura E, Inagaki K, Toma K, et al. Mutual interaction of kisspeptin, estrogen and bone morphogenetic protein-4 activity in GnRH regulation by GT1-7 cells. Mol Cell Endocrinol. 2013;381(1-2):8-15.
102. Gruson D, Dabla P, Stankovic S, Homsak E, Gouget B, Bernardini S et al. Artificial intelligence and thyroid disease management: considerations for thyroid function tests. Biochemia Med. 2022;32(2):182-8.
103. Lowery JW, Rosen V. Bone morphogenetic protein–based

therapeutic approaches. Cold Spring Harb Perspect Biol. 2018;10(4):a022327.

104. Giorgini F, Di Dalmazi G, Diciotti S. Artificial intelligence in endocrinology: a comprehensive review. J Endocrinol Invest. 2024;47(5):1067-82.

105. Lee S, Kim J, Park SW, Jin S-M, Park S-M, et al. Toward a fully automated artificial pancreas system using a bioinspired reinforcement learning design: In silico validation. IEEE J Biomed Health Inform. 2020;25(2):536-46.

106. Perera N, Ritchie RH, Tate M. The role of bone morphogenetic proteins in diabetic complications. ACS Pharmacol Transl Sci. 2019;3(1):11-20.

107. Sun Q, et al. Serum adiponectin levels are positively associated with diabetic peripheral neuropathy in Chinese patients with type 2 diabetes. Frontiers in Endocrinol. 2020;11:567959.

108. Carlson WD, et al. A process for the design and development of novel bone morphogenetic protein-7 (BMP-7) mimetics with an example: THR-184. Frontiers in pharmacol. 2022;13:864509.

109. Lundberg SM, Lee S-I. A unified approach to interpreting model predictions. Advances in neural information processing systems. 2017;30.