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Review Article

What do we currently know from *in vivo* bone strain measurements in humans?

P.F. Yang[1,2,3], G-P. Brüggemann[2], J. Rittweger[1]

[1]Division Space Physiology, Institute of Aerospace Medicine, German Aerospace Center, Cologne, Germany; [2]Institute of Biomechanics and Orthopaedics, German Sport University Cologne, Cologne, Germany; [3]Key Laboratory for Space Bioscience and Biotechnology, Faculty of Life Sciences, Institute of Special Environmental Biophysics, Northwestern Polytechnical University, Xi'an, China

Abstract

Bone strains are the most important factors for osteogenic adaptive responses. During the past decades, scientists have been trying to describe the relationship between bone strain and bone osteogenic responses quantitatively. However, only a few studies have examined bone strains under physiological condition in humans, owing to technical difficulty and ethical restrictions. The present paper reviews previous work on *in vivo* bone strain measurements in humans, and the various methodologies adopted in these measurements are discussed. Several proposals are made for future work to improve our understanding of the human musculoskeletal system. Literature suggests that strains and strain patterns vary systematically in response to different locomotive activities, foot wear, and even different venues. The principal compressive, tension and engineering shear strain, compressive strain rate and shear strain rate in the tibia during running seem to be higher than those during walking. The high impact exercises, such as zig-zag hopping and basketball rebounding induced greater principal strains and strain rates in the tibia than normal activities. Also, evidence suggests an increase of tibia strain and strain rate after muscle fatigue, which strongly supports the opinion that muscle contractions play a role on the alteration of bone strain patterns.

Keywords: Bone Strain, *In vivo*, Bending, Strain Gauge, Muscle Fatigue

Introduction

It is well accepted that bones adapt to different types of loading, e.g. by various exercises or by disuse, the former being followed by anabolic responses and the latter by bone losses. Literature suggests that specific exercises or training can improve people's bone mass and strength[1]. On the other hand, disuse during space flight was shown to induce a loss of more than 2% in hip trabecular volumetric bone mineral density (vBMD) per month[2]. Inevitably, bone deformation will be induced by dynamic loading (because the static bone loading rarely happens *in vivo*, it is not included in this discussion). The effects of the various factors involved in bone loading, which include strain magnitude, strain rate, and the number of loading cycles are well documented[3-4]. Strain magnitude (symbol: ε or $\mu\varepsilon$) which refers to the extent of bone deformation is easy to understand. Strain rate (symbol: ε/s or $\mu\varepsilon$/s) is the rate of strain change per unit of time, or more simply, the rapidity with which strain alterations occur. Evidence from animal studies indicates that strain rate can constitute an osteogenic stimulus independent of strain magnitude[5-6].

It is commonly thought that both ground reaction force (so called weight-bearing) as well as forces arising from muscular contraction contribute to the loading of the leg bones. Importantly, biomechanical analyses suggest that, of the two, the larger forces are caused by muscular contractions[7]. Moreover, there are co-contractions of ago-antagonistic muscle systems in virtually all motion patterns. Therefore, mere estimations of bone deformation by assessment of external loading and inverse dynamics approach can not provide a full account of the relationship between bone strains and osteogenic bone response. Even though the importance of bone strain for bone metabolism has been realized, knowledge of *in vivo* bone strains during habitual physical activities and specific exercises is very limited.

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Corresponding author: Peng Fei Yang, Division Space Physiology, Institute of Aerospace Medicine, German Aerospace Center, Linder Höhe, D-51147 Cologne, Germany
E-mail: Pengfei.Yang@dlr.de

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With development of the methodology of *in vivo* bone strain measurements it has become possible to record bone deformation under physiological conditions. A number of *in vivo* animal studies provide compelling quantitative evidence for the relationship between bone strain and osteogenic response. In these studies, different methods for *in vivo* bone strain measurement have been applied.

It has to be considered, though, that *in vivo* bone strain measurements are invasive and technically challenging. Nevertheless, the first pioneering study in humans stems from 1975[8] and the bulk of the currently available studies started from 1996 onwards. Today there are a total of approximately 40 subjects of whom *in vivo* bone strain data have been published. However, there are a couple of important questions that have still not been addressed, which is the subject of the following appraisal.

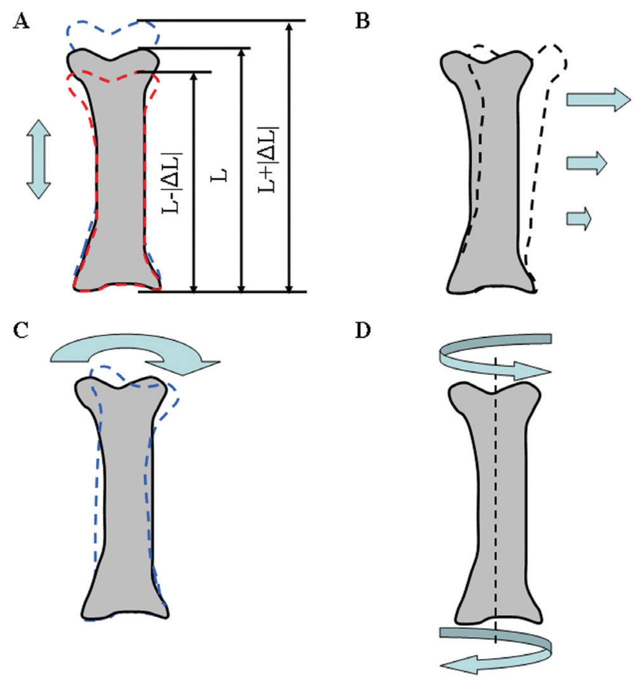

Figure 1. Different types of bone strain. **A**: axial strain; **B**: shear strain; **C**: bending strain; **D**: torsion strain.

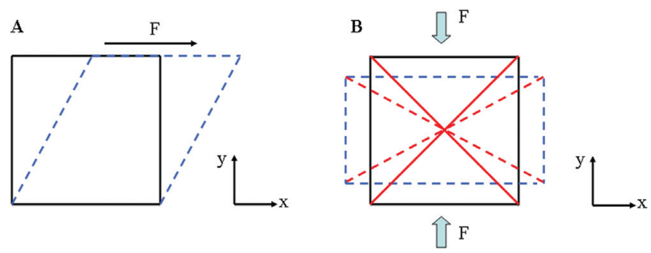

Figure 2. Shear strains. These are due to a two-dimensional geometric deformation of an infinitesimal material element (plain black line: original geometry, dashed blue line: sheared geometry). **A**: simple shear. **F**: shear force exerted on the infinitesimal material element; **B**: pure shear. There is pure shear along the diagonals of the element (plain red lines: original diagonals, dashed red lines: sheared diagonals). **F**: compression force exerted on the element.

Type of bone deformation

Strain is the geometric deformation within the material. One way to measure it is by strain gauges. Strain is expressed as the ratio between the length change and original length, and it is therefore given as a dimensionless number.

According to the following equations:

Compressive strain: $$\varepsilon_{compressive} = \frac{L - L_o}{L_o} = \frac{-|\Delta L|}{L_o} \quad (1)$$

Tensile strain: $$\varepsilon_{tensional} = \frac{L - L_o}{L_o} = \frac{|\Delta L|}{L_o} \quad (2)$$

Where L_O: original length; L: current length; $|\Delta L|$: length change. According to above equations, compressive strain and tensile strain are negative and positive values, respectively.

Strain can be simply tensile or compressive (axial strain, Figure 1A). More complex strains are generated by e.g. two planes sliding over each other (shear strain, Figure 1B), by bending (bending strain, Figure 1C) or by rotation (torsion strain, Figure 1D).

Axial strain

Axial strain is, by definition, a strain in the same direction as the applied load . Both compressive strain and tensile strain are axial strains. For long bones, axial strain under physiological conditions is mostly along the long axis of the bone.

It is generally thought that compressive and tensile strains are the main component for most kinds of activities.

Shear strain

When loading a solid material, there will always be both compressive and tensile strains, with a certain angle between them. In any direction within this angle, shear strain exists along the surface of the structure.

Generally, the distortion in shear can be described as the combination of two ideal types of strain: simple shear (Figure 2A) and pure shear (Figure 2B). The sum of these two shears is equal to the so called engineering shear strain which is defined as the angle change between two lines initially perpendicular to each other in the non-deformed or initial configuration. Because the engineering shear strain is equal to the difference between two principal strain values, it can conveniently be calculated and has frequently been reported in literature[9-12]. As expected, shear strain was found during almost all activities, such as walking, running, and hopping.

Bending strain

Bone bending strain is induced by the external force or force component which is applied perpendicular to the longitudinal

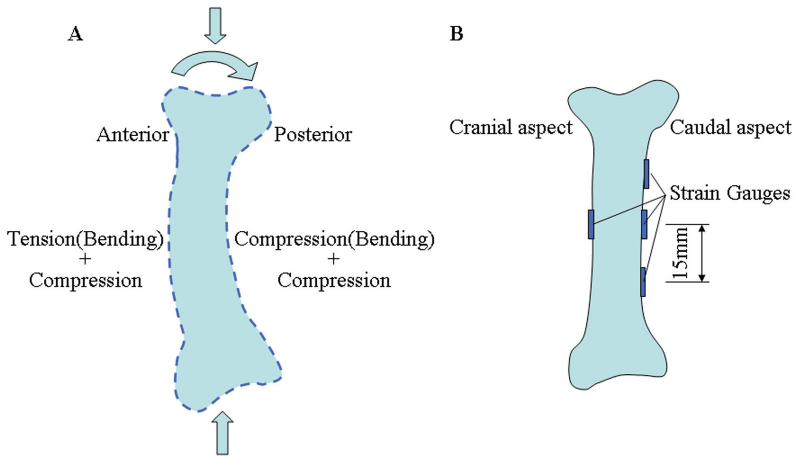

Figure 3. A: Bending superimposed with axial compression; **B**: As a demonstration of bending strains in previous study, strain gauges were attached on both side of the radius in goat[14].

axis of the bone. The external force can be due to eccentric (off-axis) loading, and also due to axial force acting about a bone's longitudinal curvature[13]. The bending strain may cause tension in one part (e.g. anterior aspect) of the bone and compression in the opposite part (e.g. posterior aspect) of the bone (Figure 3A). Normally, the bending strain is superimposed with axial compressive strain (Figure 3A), and the question arises how bending and principle strain magnitude compare to each other.

Some evidence, however, does exist to account for the presence and magnitude of *in vivo* bending strains in the human body. For example, it has been observed during zig-zag hopping that the angle of maximum principal compression to the long axis of tibia varies considerably, much more than during walking and jogging[12]. The most likely explanation for that angle change seems to be variation induced by bending moments during intense exercise, such as zig-zag hopping. However, no direct or quantitative *in vivo* bending strain data are as yet available in humans .

Torsion

Finally, there is a possibility of torsional loading on bone if the long axis of bone is twisted (Figure 1D). Assuming the long axis of the bone as 0°, the orientations of torsion strain in relation to the long bone axis will be at 45° or -45°, respectively, depending on the twisted direction of the long axis. For example, torsion of tibia is produced by the combination of ground frictional force relative to the foot and the resulting moment. Bones are generally weak in shear, and shear is typically induced by torsion or bending. In *ex vivo* testing, the fatigue strength of bovine compact bone under torsion loading is about half of the compressive fatigue strain for the same material[15]. According to Taylor et al.[15], the largest part of shear strain arises from torsion, whilst transverse tensile stress *in vivo* is rare. Shear strain induced by torsion might therefore play an important role in bone fatigue fracture.

The methodology adopted for *in vivo* bone strain measurements

The development of appropriate bonding and recording methods made it possible to assess bone strain *in vivo* in animals and humans. Since the 1940s, scientists have started to establish and apply different methods for measuring bone strain *in vivo*[16]. Although several methods have been developed during the past few decades, only two of them (strain gauges and bone staples) have successfully been applied in the human body as so far. The development of these methods will be discussed in the following.

The first generation: Strain gauges method

The principle and the procedure of strain gauges measurements

As the gold standard of material strain and stress analysis, electric resistance wire strain gauges have been use in most *in vivo* bone strain measurement studies.

Their principle is based on the fact that the electrical resistance of a specially designed wire increases with increasing strain, and that it decreases with decreasing strain. When strain gauges are firmly attached on a material, they are assumed to undergo the same deformation as the material, and measurement of the electrical resistance, then allows the assessment of strain . However, a single wire strain gauge can measure strain in one direction only. In order to measure the strain with unknown directions, rosette strain gauges (Figure 4) have to be used. In that case, the principal strain and the angle between the grid of strain gauge and the principal strain can be calculated. The details about the rosette strain gauges can be referred to the technical notes from manufactures[17].

A series of original investigations and review papers in the 1970s have described how the strain gauges should be prepared and correctly used in bone strain measurements *in vivo*[18-20]. Some modifications were also made for improving the bonding

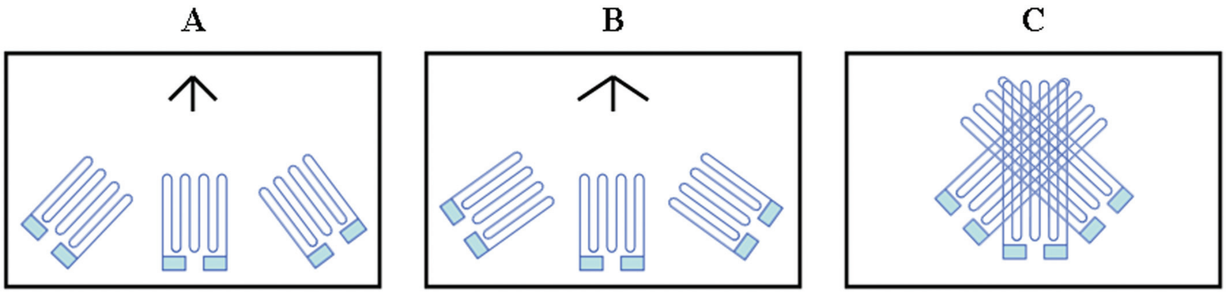

Figure 4. Basic types of rosette strain gauges: (**A**) 45° rectangular rosette strain gauges; (**B**) 60° delta rosette strain gauges; (**C**) Stacked construction rosette strain gauges. Three strain gages are placed together in a “rosette”-like layout with each gage oriented in a different direction. When the strain direction is unknown, the principal strains and their direction can be calculated by the signal from three strain gauges of rosette strain gauge.

quality *in vivo* at a later stage[21]. So far, most *in vivo* bone strain measurement approaches have used such strain gauges, even though some modifications have been made (refer to the discussion of bone staples methods). With rosette strain gauges bonded directly to the bone surface, Lanyon LE et al. and Burr et al. performed the first and second *in vivo* bone strain recording in humans, respectively[8-9]. The general procedure for implanting strain gauges during that study is described as following: The tissue overlying the proposed gauges site of the leg was anaesthetized first, and then a 5-10 cm long incision down to the periosteum was made. Part of the periosteum was removed and the bone surface cleaned. Next, the strain gauges were glued on the prepared bone surface with adhesive (isobutyl 2-cyanoacrylate monomer or polymethyl methacrylate). Then the wire of strain gauges were passed out of the wound and sutured to the periosteum. Importantly, the operation in that study took approximately 1 hour, but the strain gauge could stay thereafter for 3 days for data collection.

In Burr’s and Milgrom’s paper, degreasing of bone surface with alcohol and scoring with a bone punch are reported, as additional measures to improve strain gauge bonding[9,22]. The strain gauge signal was recorded with a portable analog tape recorder in that study, which allowed the subjects a greater degree of mobility. No pain or discomfort was reported.

Disadvantages of strain gauges

Bonding problems: Technically, the surface for bonding strain gauges should be chemically clean (i.e. free of oil, greases, organic contaminants and soluble chemical residues), water proof and sufficiently rough. However, it is almost impossible to reach these harsh conditions by preparation *in vivo*, especially during long time recordings. In the study of Burr et al., strain gauges from one of two subjects were not firmly attached when they were checked after recording, and the data from this subject had to be abandoned[9]. Even without significant debonding, there is no way to evaluate the bonding stability *in vivo*. The bonding quality is the key point for the accuracy of foil strain gauges. Insecure bonding is likely to result in under-estimation of strain values.

Bending strain: Assessing bending strains with strain gauges is feasible only with a set of two rosette strain gauges attached on two opposing aspects of bone[23]. In a study by Biewener et al.[14], for example, the strain gauges were bonded on the cranial and caudal aspect of the radial and tibial diaphysis of goats (Figure 3B). Then, the ratio between the compressive strain due to bending and axial compression in three goats during gait at a constant speed (up to 5 m/s) was calculated, as 8.1 for the radius and 11.6 for the tibia. Furthermore, this ratio did not change significantly throughout the speed range. This suggests that bending is the predominant strain in bone during gait. Unfortunately, such an approach is hardly feasible for the human body, in particular for the tibia, as it is by virtue of the human anatomy quite impossible to attach a pair of strain gauges on two opposite sides of a bone, without destroying muscles. However, the axial and bending strain of bone can not be distinguished with strain gauge attached on one side of a bone only. Accordingly, there are as yet no measurements in human body to provide *in vivo* bone 3D deformation.

Temperature drift: Temperature related effects are the most common cause of error in the application of strain gauges. This is because electrical resistance is dependent on temperature. For obvious reasons, using two or more strain gauges *in vivo* in order to compensate for the effect of temperature, as one would do in an engineering scenario, is not feasible.

Calibration: For the strain gauges, the purpose of calibration is to develop an accurate relationship between the output voltage and bone strain. The calibration procedure is a cumbersome business, because of the potential affects of the implantation procedure[24], the linearity of strain gauges and the length of lead wire required for strain gauges (the wire cables which connect the strain gauges to the Wheatstone bridge. When the strain gauges are remote from the recording instrument, the resistance of wire cable has to be taken into account)[25].

The second generation: Extensometers and bone staples with strain gauges

Obviously, there is a desire to reduce the invasiveness of direct bonding of strain gauges to bone. To this effect extensome-

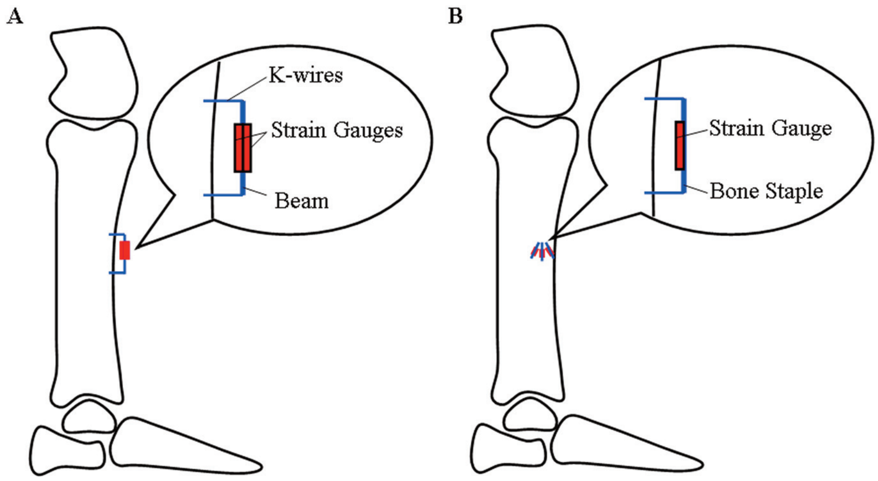

Figure 5. Diagram of extensometer and strain gauged bone staples in bone. The principle idea is to create a mechanically stable link between the bone and the extensometer to isolate strains in the extensometer. **A**: extensometer which was only able to record axial strain; **B**: strain gauged bone staples in 30° rosette pattern which was able to record axial and shear strain. Blue line: bone staples. The strain gauges were glued on the undersurface of the staples[12].

ters have been developed that can be externally mounted on two K-wires placed percutaneously into the bone cortex. The underlying idea is to isolate the deformation in a measurement device that is stably mounted on the bone. Before inserting the K-wires, local anesthesia is administered. Next, two K-wires are affixed into the predrilled holes to a depth of 4 mm, so that the extensometer can be mounted on the K-wires. The extensometer is composed of a bronze beam with two pairs of strain gauges bonding to the top and the bottom surface of the beam, respectively (Figure 5A). Bone strains are then transmitted to the beam' strain gauges through the K-wires. Again, strain gauges are connected to the recording device via cable connection. Unfortunately, however, this approach seems to generate artifacts induced by e.g. the heel strike, and it seems to generate smaller strain value readings than the classical strain gauge approach[26-28].

Based upon the same principle, commercial bone staples with instrumented strain gauges have also been used[29]. Subsequently, Milgrom C. et al. modified this method and included three strain gauges into three bone staples in a 30° rosette pattern (Figure 5B)[30]. Obviously, this requires additional holes in the tibia, which causes a practical problem related to increased invasiveness, as well as a theoretical problem related to possible effects of the holes upon structural rigidity of the instrumented bone. On the other hand, principal compressive and tensile strain as well as engineering shear strain can be conveniently calculated with this set up.

Compared to strain gauges glued directly onto the bone, the application of bone staples resolves the bonding problem. Moreover, this technique requires less invasive surgery for the subjects because the periosteum is mostly left intact. However, gauge failure or damage due to the surgery occurred very often[10].

Results from *in vivo* bone strain measurements in humans

Results from *in vivo* bone strain measurements in humans have been summarized in Table 1.

Bone strain induced by different activities

To date, most *in vivo* bone strain measurements focus on the human tibia. Pioneering work was done by Lanyon and co-workers as early as in 1975[8]. With a rosette strain gauge attached to the anteromedial aspect of tibia midshaft, tibia strains were recorded during walking on a treadmill and on the floor. The principal strain and strain angle relative to the tibia's long axis were calculated. The strain magnitude when walking was found to be approximately -430 με ('-': compression strain) during heel off to toe off, but up to 850 με ('+': tensile strain) when running during toe strike to toe off. As commented by D.B. Burr et al.[9], that work demonstrated the general possibility of such strain recording in humans.

Almost 20 years later, after the development of a portable strain measurement system, Burr et al. performed the second *in vivo* human tibia strain measurement during vigorous activity[9]. Data from this investigation indicate that the greatest principal strains and engineering shear strain during most vigorous activities (jogging, sprinting, running, zigzag running) were significantly higher than those during walking. The greatest strain was engineering shear strain which occurred during zigzag uphill and downhill running (approximately 2000 με). For strain rate, the greatest compressive, tensile and engineering shear strain rate was recorded during sprinting on a level surface. By contrast, the strain rate during walking is much smaller than those of running (see also Table 1 and 2). Burr's study gave us the first comprehensive impression about the *in vivo* tibia strain in human during vigorous activities.

Table 1. Overview of *in vivo* bone strain (tibia, metatarsal and radius) results in humans.

Study	Type of exercises	Peak Strain (με)			Peak Strain Rate (με/s)		
		Com. (-)	Tension (+)	Shear (+)	Com.	Tension	Shear
Tibia							
Lanyon LE et al. 1975	Walking	30-850	30-580	-	-	-	-
Burr DB et al. 1996	Walking, Jogging, Sprinting, Zigzag running	400-1300	380-750	700-2000	7000-30000	7000-20000	13500-50000
Milgrom C et al. 1996	Walking and running with different shoes	400-1000	540-680	760-1500	2200-14000	-	-
Rolf C et al. 1997	Forward jump with forefoot and heel landing	-					
Fyhrie DP et al. 1998	Walking before and after exhaustion	-					
Mendelson S et al. 1998	Walking with and without cane	Axial peak to peak strain: 65-230			270-2500	-	-
Milgrom C et al. 1998	Walking and running with different shoes	-					
Milgrom C et al. 2000	Running, Drop jump	1900-2100	900-1000	5300-7400	9600-13000	4800-7600	28500-50900
Milgrom C et al. 2000	Running, Cycling, leg press	290-1700	270-1400	630-5000	1500-1000	1300-8200	4500-38000
Milgrom C et al. 2000	Walking, Running, Basketball rebound	560-3200	700-1600	1200-9000	4300-19000	3700-7400	12500-58000
Milgrom C et al. 2001	Walking, Jogging, jump, Hopping	250-2200	500-2200	400-4100	2000-8000	2500-16000	5000-25000
Milgrom C et al. 2001	Walking with four different shoes	700-1200	460-720	1250-2600	6200-6500	2800-4000	12700-16000
Ekenman I et al. 2002	Walking and running with different shoes	Axial peak to peak strain: 1000-2400			3000-15000	4200-15600	-
Milgrom C et al. 2002	Walking, Jogging, broad jump, Vertical jump	360-700	160-1250	-	2500-8300	2100-14000	-
Milgrom C et al. 2003	Running at treadmill and on asphalt	400-2500	650-1250	-	3200-15000	3200-17000	-
Milgrom C et al. 2007	Before and after fatigue (2 km run, 30 km march)	470-720	340-610	-	3700-4700	4400-5600	-
Metatarsal							
Milgrom C et al. 2002	Walking, Jogging, Jumping	2600-2700	230-1100	-	9800-46000	3400-12000	-
Arndt A et al. 2002	Walking before and after fatigue	1500-2200	140-440	-	4200-5500	-	
Radius							
Földhazy Z et al. 2005	Arm curl, Chin up, Fall, Push up, Stirring, type writing, vacuuming carpet and wrist curl	0-6000	0-1500	-	0-85000	-	-

Table 2. Overview of *in vivo* bone strain studies in humans.

Study	N	t	Aim	Methods and site	Type of exercises	Output
Lanyon LE et al. 1975	1	3d	Tibia strain recording	Foil 45° rosette SG Anteromedial aspect of tibial midshaft	Walking on treadmill or the floor, with or without shoes, with 0, 21, 45, or 71kg weights	**1.** Walking: The end of swing period, prior to 'heel strike', principal CS > principle TS, in line with long axis; **2.** Swing forward: strain pattern reversed; **3.** Wearing shoes (swing phase): deformation increased and decreased when foot was on the ground; **4.**Walking on a concrete floor with increasing loading: angle pattern keep constant, **5.** Between 'full foot' and 'heel off', strain increased greatly. **6.** Running without shoes: larger deformation during stance phase of running than when compared to walking.
Burr DB et al. 1996	2	<1d	Tibia strain during vigorous activities	45° rosette SG Medial tibial midshaft	Walking (5 km/h) Jogging (10.15 km/h) Sprinting(13.38km/h) Walking with 17kg load Walking or running, zigzag running uphill, downhill	**1.** Principal CS: -414 με (downhill walk)~-1226 με (zigzag-run uphill) **2.** Principal TS: 381(walking + 17kg) ~743 με (zigzag run uphill) **3.** SS: 1583με (sprinting)~871 με(walking) **4.** Highest CSR and TSR: sprinting and downhill zigzag run and smallest when walking **5.** Highest SSR: sprinting, downhill running

Table 2. (cont.)

Study	N	t	Aim	Methods and site	Type of exercises	Output
Milgrom C et al. 1996	2	<1d	Compare the tibia strain when subjects wearing different shoes	45° rosette SG Medial tibial midshaft	Walking at 3miles/h with shoes: **1.** Rockport prowalker 7580 **2.** New balance running shoes **3.** Light Israeli infantry boots **4.** 2 layer sole infantry boots **5.** Zohar infantry boots Running on the track (50m/11s) with the 2nd, 3rd and 5th shoes	During walking **1.** Zohar infantry boots had lowest principal CS and CSR; **2.** New balance running shoes had lowest SS; **3.** no single shoe lowered all the strain and SR; During running, zohar boot had lowest strain and SR.
Fyhrie DP et al. 1998	7(6)	<1d	Fatigue, tibia strain and age	extensometer (SG) Anteromedial tibial midshaft	5 km/h Walking before and after exhaustion exercise	**1.** Tibia strain depicts a increase after muscle fatigue in old people, but have no change in young people; **2.** Heel strike impact is increased in young people, but decreased in old people after muscle fatigue;
Mendelson S, et al. 1998	7(6)	<1d	Tibia strain and cane usage	extensometer (SG) Anteromedial tibial midshaft	Walking without cane Walking with cane in right hand Walking with cane in left hand	**1.** Cane did not reduce the peak to peak tiabial axial strain: 170, 169 vs. 148 με **2.** However, cane usage reduced the max. tibial tibial CSR: 1048, 794 vs. 757 με/s
Milgrom C et al. 1998	7(6)	<1d	Compare the shoes' effect on tibia strain	extensometer (SG) Anteromedial tibial midshaft	Walking (5 km/h), run (16.3 km/h): **1.** Nike Air Max running shoes **2.** Zohar sport shoes **3.** Two layers' sole infantry boots	**1.** Walking: Zohar shoe had lowest CS, TS and CSR, TSR; **2.** Running: No differences on CS, TS and SR between these shoes; **3.** No difference on CS, TS and SR between walking on corridor and on treadmill
Milgrom C et al. 2000	6(4)	1d	Tibia strain during high impact exercise and running	Bone staples in rosette pattern (SG) Medial aspect of midtibial diaphysis	Running at 17 km/h Drop jump (26, 39 and 52 cm)	**1.** No difference in CS, TS and SS with increasing jump heights, but CSR decreased; **2.** No relation between max. principal CS and jump potential energy; **3.** No difference between the principal strain during running and jumping from 52 cm (up to ~5500 με), but TSR higher during running.
Milgrom C et al. 2000	6	1d	Evaluation of potential strengthening exercise with tibia strain	Bone staples in rosette pattern (SG) Medial aspect of mid tibial diaphysis	Running on cinder track at 17 km/h; Running on treadmill at 5 km/h; Cycling at 60 c/s, power 100W; Stepmaster, aerobic mode 4, 5 min; During leg press.	**1.** No difference in principal TS, CS and SS between walking, leg press or stepmaster; **2.** Higher strain during running than walking; **3.** TSR and SSR are lower in cycling than walking; **4.** Max. TSR during walking were higher than leg press, stepmaster and cycling; **5.** Highest max. CS and SS during running, during walking were higher than cycling and leg press. **6.** From the view of bone strain, only running is effective strengthening for tibia.
Milgrom C et al. 2000	3	1d	Assess bone strain developed during sporting activities	Bone staples in rosette pattern (SG) Medial aspect of midtibial diaphysis	Walking at 5 km/h Running at 17 km/h Performing basketball rebound	**1.** The principal CS, TS and SS during running were 2 to 4.5 times those of walking, but those during basketball rebounding were 2.25 to 7.41 times greater than during walking. **2.** The TSR, CSR and SSR during rebounding and running were 2.16 to 4.60 times higher than during walking

Table 2. (cont.)

Study	N	t	Aim	Methods and site	Type of exercises	Output
Milgrom C et al. 2001	2	1d	Assess the bone strain induced by lower limb indoor exercise compared with those of walking	Bone staples in rosette pattern (SG) Medial aspect of midtibial diaphysis	Free walking; Jogging at 17 km/h; Vertical jump on two legs to 5 cm; Standing broad jump to 20 cm; Hopping 50 cm on right leg; Zig-zag hopping on the right leg.	Male: **1.** Highest CS: jogging, hopping 50 cm and zig-zag hopping; **2.** Highest TS: jogging, vertical jump on right leg to 5cm, hopping 50 cm and zig-zag hopping; **3.** Highest SS: hopping 50cm and zig-zag hopping; **4.** Highest SSR: jogging; **5.** Highest CSR and TSR: zig-zag hopping; **6.** Lowest SR and compression strain: Walking Female: **1.** Highest CS and TS: zig-zag h opping; **2.** Highest SS: vertical jump on right leg to 5 cm, hopping 50 cm and zig-zag hopping; **3.** Highest CSR and TSR: zig-zag hopping; **4.** Highest SSR: jogging, standing broad jump to 20 cm and hopping to 50 cm; **5.** Lowest strain and SSR: walking
Milgrom C et al. 2001	3	1d	Test the influences of shoe sole composition on bone strain and strain rate	Bone staples in rosette pattern (SG) Medial aspect of midtibial diaphysis	Walking at 5 km/h with shoes: **1.** 65 shore A polyurethane (SAP) **2.** 65 SAP with heel air cell **3.** 75 SAP **4.** Composite of 40 and 65 SAP	CS, SS and shear SR is lower with air cells embedded shoes; Lower TS and CSR with 75 SAP shoes; Lower SS rate with air cells embedded shoes;
Ekenman I et al. 2002	9		Access the influence of running shoes and military boots with shoe orthoses on bone strain	Bone staples in rosette pattern (SG) Medial aspect of middle and distal tibial diaphysis	Walking 5 km/h before and after run; Running shoes and army boots with and without semirigid and soft orthoses: walking 5 km/h; Run 2km (13 km/h) + running shoes Run 1km +army boots;	Before running: Walking: higher peak to peak axial (p-p) strain with boots than running shoes; lower p-p strain with orthoses; soft orthoses with boot lowered the TSR and CSR; Running: p-p strain with boots was not higher than running shoes; semirigid orthoses with boots increased TSR and CSR; walking again after running: No increase in TSR and CSR compared with before running; Shoe orthose may be warranted for fracture during mostly walking exercise, but not mostly running exercise.
Milgrom C et al. 2002	2	1d	Compare the strain in second metatarsal with the tibia and access the effect of shoe gear on these strain	Bone staples with two perpendicular SG • Medial aspect midtibial diaphysis • Dorsal surface of mid 2nd metatarsal diaphysis	**1.** Walking at 5 km/h **2.** Jogging at 11 km/h One subject: 50 cm broad jump Vertical jump to 10cm (one leg) Vertical jump to 10 cm (two legs)	Barefoot walking: **1.** Peak axial metatarsal CS, TS, SR > those of tibia **2.** Barefoot jogging: **3.** Peak metatarsal CS and SR > those of tibia; **4.** Peak axial CS reach 5677 με; Wearing running shoes: **1.** Metatarsal strain lower, but not tibia compression strain; **2.** Tension strain increased; **3.** Metatarsal CS, TS and SR > those of tibia; **4.** Broad jumping, vertical jumping: strain>3000 με;

Table 2. (cont.)

Study	N	t	Aim	Methods and site	Type of exercises	Output
Arndt A et al. 2002	8	<3h	Evaluate the effect of muscle fatigue on metatarsal strain	Bone staples with two perpendicular SG Dorsal surface of mid 2nd metatarsal diaphysis	Walking barefoot (3 km/h) until Fatigue: Pre-fatigue without 20 kg backpack; Pre-fatigue with 20 kg backpack; Post-fatigue without 20 kg backpack; Post-fatigue with 20 kg backpack;	Pre-fatigue, no backpack: **1.** Toe down was followed by peak tension (8±7%), followed by max. compression (65±15%), immediately after, compression decreased to about zero; **2.** Mean peak CS: -1534±636με, TS: 346±359με; SR: 4165±1233με/s; **3.** Peak compression during baseline without backpack less than other condition; **4.** SR increased with backpack but not post-fatigue; Post-fatigue: **1.** Peak tension decreased with backpack; **2.** Time of peak CS was later for post fatigue without backpack; **3.** Peak TS occurred earlier without backpack;
Milgrom C et al. 2003	3	1d	Determine the tibia strain difference during treadmill and overground running	Bone staples with one SG Medial aspect of the mid tibial diaphysis	With Nike Air Max shoes: Running at 11km/h at treadmill Free running on asphalt at 11 km/h;	Peak mean axial CS and TS, peal mean TSR and CSR were higher during running on overground than on treadmill; **1.** Overground: CS: 1957 με, SR: 12876 με/s; TS: 1273 με, SR:14160 με/s **2.** Treadmill: CS: 664με, SR: 3346 με/s; TS: 860με. SR: 6645 με/s.
Földhazy Z et al. 2005	10	<2h	Evaluate the radial strain with different type of exercises	Bone staples with two perpendicular SG distal radial metaphysis	Arm curl with 7 kg Chin up; Fall, standing and kneeling; Push up on knee; Stirring; Type writing; Vacuuming carpet; Wrist curl in extension with 2 kg; Wrist curl in flexion with 2 kg;	**1.** Max. CS for falling and push up > for the others (except falling on knee vs. arm-curl and wrist-curl); **2.** Max. TS for chin-up > for arm-curl, fall kneeling, push up, stirring and typing; **3.** For push-up: there is no any tension, p-p strain around 2300 με; **4.** Median value of strain rate: for falling (from standing: 45954 με/s, on kneeling: 18582 με/s) > for the other activities;
Milgrom C et al. 2007	4		Evaluate the effect of muscle fatigue on tibia strain	Bone staples in rosette pattern (SG) Medial aspect of midtibial diaphysis	Before and after fatigue: Max. right GM isokinetic torque, Tibia strain, force plate measure; Fatigue procedure: 1. 2 km run (>12 km/h) 2. 30 km march (6 km/h)	After the march: **1.** The peak GM isokinetic torque was reduced by 37%, 31%, 21% and 23% respectively; **2.** TS: 26% increased post run and 29% increased after march; **3.** TSR: 13% increased post run and 11% increased after march **4.** CS: 15% decreased post run and 24% decreased after march; **5.** CSR: 9% increased post run and 17% increased after march;

N: number of the subject; t: time period of the study; SG: strain gauges; CS: compression strain; TS: tension strain; SS: shear strain; CSR: compressive strain rate; TSR: tension strain rate; SSR: shear strain rate;

Moreover, the principal compressive, tension and engineering shear strain, compressive strain rate and shear strain rate in the tibia during running on a cinder track were found to be significantly higher than those during walking, which was seen as baseline due to its minimal bone remodeling[11]. Surprisingly, during running, the principal strains are comparable to those during high impact exercise (drop jump), and the strain rate seems to be even higher in running than during the drop jump exercises[10]. All of the above running data were based on running on cinder track. Much lower axial principal strains and strain rates were reported in literature during treadmill running[31].

However, compared to running, walking, vertical jump and hopping, higher principal strains and strain rates in the tibia were found during other kinds of high impact exercises, such as zig-zag hopping[12], and even more so during basketball rebounding, where the greatest values of principal compression, tension and shear strain during rebounding were about 2 to 7 times greater than those during walking. The strain rates were approximately 2 to 5 times higher than during walking[30].

As mentioned in the 'methodology' section, three methods were adopted in the previous studies in tibia strain recording: strain gauges directly bonded onto the tibia, the extensometer method and the approach with bone staples. With the extensometer method, the range of tibial strains observed during walking was approximately one third of the strains recorded with strain gauge directly bonded to the tibia[26]. The discrepancy between methods can arise in several ways. Firstly, the stability of the K-wire inside the tibia was not checked during the measurements. Second, there is a possibility of artefacts induced by K-wires bending during the measurements. On the other hand, the two approaches (directly bonded strain gauges and staples) yielded very similar results during walking. This suggests that the bone staple may be a quite efficient substitute for the method of direct bonding to bone surface under certain circumstances[9,32].

Besides the tibia, the metatarsal is another common site of study. It is of specific interest because it is a common site for fatigue fractures. Few studies have recorded the human metatarsal strain during different locomotive activities. The results indicate that peak axial metatarsal compressive and tensile strains, as well as strain rate are significantly higher than those in the tibia during treadmill walking. Moreover, high strains seem to also occur when subjects are jogging barefoot (Table 2). During jumping on one and two legs, the tensile and compressive strains exceeded 3000 $\mu\varepsilon$[33]. These data may indicate that the metatarsals have a much higher fatigue fracture incidence than the tibia because of the greater strains that they are typically exposed to.

To the best of our knowledge, there is only one *in vivo* strain recording available in the human upper extremity, namely in the distal radial metaphysis. Ten different activities, mainly with upper extremity, were studied, including arm curl, chin up, fall forward from standing and kneeling, push up, wrist curl in extension and flexion with 2 kg weight. Results indicate that the largest radius tensile strain occurs during chin up. Conversely, there was no tensile strain in the radius observed during arm curl, fall or push up exercise. Among all those activities, falling and push up exercises resulted in the largest compressive strain, which amounted to up to -6000 $\mu\varepsilon$ and -4300 $\mu\varepsilon$, respectively[34].

External factors influencing bone strain and strain rate

As often advertised for running shoes, the soft soles or embedded air cells in shoes are supposed to absorb the impulse energy from the ground reaction force. To some extent, this point of view is supported by scientific literature. As previous studies have shown, the compression and engineering shear strains were significantly attenuated with heel air cell embedded in the shoe during walking (from ~900 to ~700 $\mu\varepsilon$ and from ~1800 to ~1250 $\mu\varepsilon$, respectively). Shear strain rate also was significantly reduced by the heel air cell[32]. Similarly, results in another study suggested that soft orthoses have potential to lower the tibia tension and compressive strain rate during walking[35].

Finally, one study has investigated the effects of ipsilateral and contralateral cane use upon tibia axial strains and strain rate. Interestingly, cane usage generally failed to reduce tibial strains, but decreases in strain rate were observed[26].

From geometric evidence, close functional relationship between muscle function and bone anabolism exists[36]. Besides the ground reaction force, agonistic muscles also exert force on bone through tendons to realize the specific movement of human body. Accordingly, muscular contraction forces also seem to be a source of mechanical stimulation. Also, as the counterpart of agonistic muscles, antagonistic muscle can increase the loading on bone during 'ballistic' or 'open-loop' motor actions.

So far, only few data relate muscle activities to *in vivo* bone strain. Arndt et al.[37] reported the alteration of human second metatarsal (MTΠ) dorsal strain before and after M. flexor digtorum longus (FDL) fatigue. FDL contractions will induce dorsal tensile strains and reduce compressive deformation of MTΠ which is induced by ground reaction force and dorsiflexors during the stand phase. Part of this inference was tested in the study under discussion. Tensile strain of dorsal MTΠ surface was in close temporal relationship to activation of FDL. The peak activation of FDL occurred during the transition from MTΠ tensile strain to compressive strain during mid-stance phase. After the FDL muscle was fatigued the average peak compressive strain increased 42% and the peak tensile strain decreased 55%[37]. It seems, therefore, that the bone strain protecting capacity of FDL was attenuated after the muscle had been fatigued. Similarly, in another study, after whole body fatigue (2 km running and 30 km march), tibia strain during walking was measured. Compared to the initial conditions, the tensile strain increased and the compressive strain decreased following the run and the march, respectively (The quantitative data is shown in Table 2). The tensile and compressive strain rates also increased after fatigue (Peak gastrocnemius torque was measured in this study to assess muscle fatigue)[38]. Thus, muscular fatigue can be assumed to cause high bone strains and may therefore contribute to the development of stress fracture. In the study of Fyhrie et al., the tibia strains were assessed after the fatigue exercise. Results suggested that high strain rates were induced after fatigue in younger subjects which means that bone strain rate, in addition to strain magnitude might contribute more to the stress fracture[28]. Morever, a study by Milgrom et al. has also reported that tibia strain is significantly enhanced by fatigue, and that higher strains are to be recorded during vigorous physical activities in a fatigued state, which again underlines a possible causative role of muscle fatigue in the development of stress fracture[38].

Risk evaluation (Pain and Infection)

Most *in vivo* studies have reported swelling and tenderness at the surgical site in some subjects. These complaints did generally recover well, so that subjects were able to return to their normal activities within few weeks, except for one or two exceptions who required longer recovery (less than a few months). Another problem which has to be considered seriously is the risk of infection, especially during the application of bone staples. In previous studies, bone staples were inserted into cortical bone to a depth of approximately 4 mm to avoid penetration of the cortex, thereby reducing the infection risk. Despite this, the risk is still one of the obvious problems in bone strain *in vivo* measurements.

What should be done in the future?

As discussed above, the few *in vivo* bone strain measurements that have been done in the past decade have greatly contributed to musculoskeletal science[8-12,22,26-35,37-38]. On the other hand, these studies have given us only an incomplete impression about *in vivo* bone strain, and they were mainly limited to the tibia and metatarsal. Accordingly, there are many open questions which we can not answer.

First, there are serious limitations imposed by the current methodological approach. As mentioned above, the goal must be to improve our understanding of bone strain within the human body, and to do so in a way that is less invasive and more accurate at the same time, to ideally reveal also 3-dimensional strain information. Of interest, accurate and less invasive approaches have been proposed, although no data from human *in vivo* application are available as yet. One such approach is based upon an optical technique for non-contact, 3-dimensional deformation measurement, namely the digital image correlation (DIC). This has been employed to measure the strain distribution of animals' bone *ex vivo*. In this method, a high contrast speckle pattern (normally with painting or spraying) is applied onto the bone surface. The speckle pattern changes during loading are then optically tracked. Compared with strain gauges, this method is more informativ for anisotropic materials, such as bone. Although some *in vivo* bone strain recordings have been done in animals[39-40], further improvements are needed to avoid exposing and painting bone surface for *in vivo* bone strain measurements in human. To overcome the limitations of invasiveness in the methods mentioned above, ultrasound wave assessment was introduced to measure bone deformation[41]. Again, no *in vivo* data are available as yet. Summarizing the above discussion, from the available methods so far, there are not too many choices to assess *in vivo* bone strains in the human body. With the exception of strain gauges and bone staples which have been used in previous *in vivo* studies, a few new methods are perceivable, none of which is easy to apply. However, these new methods could have the potential to give more strain information and thus may constitute a new step in the field of bone research.

Second, the strain pattern of bone *in vivo* is not clear during locomotive activities, even in tibia and metatarsal. Besides compressive and tensile strain, torsion and bending strain are very important composition of bone strain pattern as well, the latter one was even believed to be one of the key factors in bone fracture. However, with the available techniques, no reliable data can be obtained to understand bending and torsion strains.

Third, strain gauges, as frequently used in bone surface strain measurement *in vivo* and *in vitro*, do not provide global strain distribution and 3D component of strain. From literature, almost all the strain data are recorded in one or two sites of bone which can not represent that in other bone sites. In addition, the mechanical properties of cortical and trabecular bone are different, and previous data have shown that the bone periosteal and endocortical region have different responses to the non-invasive loading[42]. This implies that the strain gradient in the radial direction of long bone should not be ignored. How to measure the inner bone strain *in vivo* is still a big challenge. Future work could yield more information about strain distribution and 3D strain, which would certainly help to improve our understanding about the relationship between bone strain and bone modeling, remodeling process.

Fourth, according the theory of 'Wolff's law', bone will optimize its structure in response to the way it is loaded. Accordingly, the strain distribution might vary between subjects with different bone architecture. For example, with micro CT scanning and finite element analyses, Rietbergen and his co-workers have suggested that differences in strain magnitude and distribution may exist between osteoporotic and healthy femurs[43]. If *in vivo* bone strain data were available from different populations with healthy and unhealthy bones, in combination with information on their bone structure, there will be more evidence to evaluate 'Wolff' law' quantitatively.

Fifth, close functional relationships between the musculature and bone were observed in many studies[43-46]. Muscle has been proposed as a primary source of mechanical stimulation for bone metabolism. If this hypothesis is true, bone strain, as an indicator of mechanical stimulation in bone, should have strong relationship with muscle activities. However, muscle activities, especially in lower leg, are also linked to ground reaction force which is also recognized as one of the sources of bone deformation. So, how much bone strain is contributed by ground reaction force and muscle activities, respectively? Some *in vivo* study suggested that more than 70% of the forces in femur during gait were resulted from muscle forces, only less than 30% derived from body weight[47]. However, there is no quantitative data available in tibia so far. Another question arising in this context is whether there are spatial and temporal relationships between muscle activities and bone strain patterns. The answer will be yes if the muscle forces do indeed play a decisive role in the loading of bone.

Conclusions

The pioneering works of Evans, Lanyon and other scientists mark the beginning of the *in vivo* bone strain research field, and extensive data have been recorded in animal studies since then. The unique data from these studies has helped to expand our understanding of the bone adaption to bone strain induced by muscle contraction and external force. However, the measurements in human body are limited by the invasiveness and complexity.

Due to the restriction of externally available specific zones of bone *in vivo*, strain measurements are limited to few locations only, for example the anteromedial aspect in the human tibia and dorsal surface in the metatarsal. According to these data, the strain magnitude in the tibia is within the range of 0-5000 με, and in some vigorous activities, such as jumping, basketball rebounding, the tibia strain magnitude can reach approximately 9000 με. Relative to strain magnitude, high rate strain is another potential stimuli factor to stimulate osteogenic responses. Depending on the specific kinds of exercise, bone strain rate is normally in the range of 1500-20000 με/s and could reach up to 58000 με/s during vigorous activities (Table 1).

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